

Predicting the risk of adverse events in children with febrile neutropenia: A validation of previously identified clinical decision rules

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Thesis presented in fulfilment of the
requirements for the degree of Master of
Medicine in the Faculty of
Medicine and Health Sciences at
Stellenbosch University



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December 2016

Declaration

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Date: December 2016

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Abstract

Purpose

The purpose of the study was to validate an existing clinical risk assessment tool (Ammann tool) to predict adverse events (AEs) in children with cancer and febrile neutropenia (FN).

Patients and methods

Patients less than 16 years of age with confirmed malignancies receiving chemotherapy and who presented to the Tygerberg hospital paediatric oncology unit, with fever (axillary temperature $> 38^{\circ}\text{C}$ twice in 24 hours or $> 38.5^{\circ}\text{C}$ once) and neutropenia (neutrophil count $< 500\text{ cells/mm}^3$) were enrolled. A risk prediction score¹ was calculated for each patient according to the Ammann rule, and AEs were documented until antibiotics had been stopped and neutropenia resolved. The risk prediction score included haemoglobin $\geq 9\text{ g/dL}$, white cell count $< 0.3\text{ g/L}$, platelet count $< 50\text{ g/L}$ and chemotherapy more intensive than acute lymphoblastic leukaemia maintenance therapy. AEs were defined as severe medical complications, microbiologically defined infection and radiologically confirmed pneumonia.

Results

There were 100 FN episodes in 52 patients, of whom 54% had haematological malignancies, 44% solid tumours and 2% central nervous system tumours (relapsed malignancies 16%). The male:female ratio was 1.8:1 with a median age of 56 months (mean age of 71 months; range 8 to 175 months). AEs occurred in 18/57 (45%) patients with a low risk (score < 9) and 22/43 (55%) with a high risk (score ≥ 9), yielding

a sensitivity of 56.8%, specificity of 65%, positive predictive value of 50% and negative predictive value of 71%. Total WCC ($p < 0.01$) and absolute monocyte count ($p = 0.05$) were significantly associated with an AE. Antibiotic-resistant microorganisms were found in 18% of microbiologically confirmed FN. There were marked differences in the patient cohorts between high-income countries versus a low- to middle-income country with a lower median age and more resistant organisms.

Conclusion

Although this study did not succeed in validating the risk assessment tool (Ammann tool), it demonstrated the important association between total WCC, absolute monocyte count and an AE during FN.

Opsomming

Doel

Die doel van die studie was om 'n bestaande instrument vir kliniese risikobepaling (die Ammann-instrument) vir die voorspelling van ongewenste gebeure by kinders met kanker en koorsige neutropenie te staaf.

Pasiënte en metodes

Pasiënte jonger as 16 jaar wat chemoterapie vir bevestigde kwaadaardighede ontvang en wat koors (okselse temperatuur $>38^{\circ}\text{C}$ twee keer binne 24 uur, of $>38,5^{\circ}\text{C}$ eenmalig) sowel as neutropenie het (neutrofieltelling <500 selle/ mm^3), is in die studie opgeneem. 'n Risikovoorspellingstelling¹ is volgens die Ammann-reël vir elke pasiënt bereken en ongewenste gebeure is aangeteken totdat antibiotika gestaak is en neutropenie opgeklaar het. Die risikovoorspellingstelling het ingesluit hemoglobien ≥ 9 g/dL, 'n witseltelling $<0,3$ g/L, 'n plaatjietelling <50 g/L, en meer intensiewe chemoterapie as instandhoudingsbehandeling vir akute limfoblastiese leukemie. Ongewenste gebeure is omskryf as ernstige mediese komplikasies, mikrobiologies omskrewe infeksie en radiologies bevestigde pneumonie.

Resultate

Daar was 100 episodes van koorsige neutropenie by 52 pasiënte, van wie 54% hematologiese kwaadaardighede, 44% soliede tumore en 2% tumore in die sentrale senustelsel gehad het (terugkerende kwaadaardigheid 16%). Die verhouding manlike tot vroulike pasiënte was 1,8:1 en die mediaanouderdom 56 maande (gemiddelde ouderdom

71 maande; ouderdomsbestek 8 tot 175 maande). Ongewenste gebeure het by 18 van die 57 pasiënte (45%) met 'n lae risiko (telling <9) en by 22 van die 43 pasiënte (55%) met 'n hoë risiko (telling >9) voorgekom, wat 'n sensitiwiteitswaarde van 56.8%, 'n spesifisiteitswaarde van 65%, 'n positiewe voorspellingswaarde van 50% en 'n negatiewe voorspellingswaarde van 70.9% opgelewer het. Die totale witseltelling ($p = <0,01$) en absolute monosietelling ($p = 0,05$) het 'n beduidende verband met ongewenste gebeure getoon. Antibiotikumweerstandige mikro-organismes is in 18% van die mikrobiologies bevestigde gevalle van koorsige neutropenie aangetref.

Gevolgtrekking

Hoewel hierdie studie nie die risikobepalingsinstrument (Ammann-instrument) kon staaf nie, het dit die belangrike verwantskap tussen die totale witseltelling, absolute monosietelling en ongewenste gebeure gedurende koorsige neutropenie aan die lig gebring. Daar was duidelike verskille in die pasiëntkohorte van hoëinkomstelande en dié van 'n lae- tot middelinkomsteland met 'n laer mediaanouderdom en meer weerstandige organismes.

Acknowledgements

First and foremost, I want to acknowledge and express my gratitude to my mentor and supervisor, Prof Mariana Kruger, for her invaluable assistance and guidance while writing this dissertation. I deeply appreciated the opportunity to attend and present our work at the International Society of Pediatric oncology (SIOP) congress.

I would also like to extend my gratitude to Dr Anel van Zyl and Prof Pierre Goussard for their guidance and advice as well as Professor Martin Kidd for assisting with the data analysis.

Thank you to every study participant and his/her family who, despite difficult circumstances, agreed to participate in my study. With this study, we hope to improve future treatment strategies to the benefit of each patient and his/her family.

Finally, I would like to thank my family for their assistance and patience while I was completing this dissertation.

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List of abbreviations

AGE – acute gastroenteritis
AE – adverse event
ALL – acute lymphoblastic leukaemia
ALTE – acute life-threatening events
AMC – absolute monocyte count
AML – acute myeloblastic leukaemia
ANC – absolute neutrophil count
APC – absolute phagocyte count
BMI – body mass index
COPD – chronic obstructive pulmonary disease
CNS – central nervous system
CRP – C-reactive protein
CVC – central venous catheter
DCMO – dilated cardiomyopathy
DVT – deep vein thrombosis
ESBL – extended-spectrum beta-lactamase
ESR – erythrocyte sedimentation rate
FN – febrile neutropenia
FP – false positive

Hb – haemoglobin
HL – Hodgkin’s lymphoma
HIV – human immunodeficiency virus

IBI – invasive bacterial infection
ICU – intensive care unit
IL – interleukin

LRTI – lower respiratory tract infection
MDI – microbiologically defined infection
MRSA – methicillin-resistant *Staphylococcus aureus*
NPV – negative predictive value
NHL – non-Hodgkin lymphoma
PCT – procalcitonin
PPV – positive predictive value

RCP – radiologically confirmed pneumonia
SIC – severe infectious complication
SMC – severe medical complication
SPOG – Swiss Paediatric Oncology Group
TB – tuberculosis
TN – true negative
TP – true positive

UK – United Kingdom
URTI – upper respiratory tract infection
USA – United States of America
UTI – urinary tract infection
VRE – vancomycin-resistant enterococcus
WCC – white cell count
WHO – World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Background and context

Childhood cancer represents 1-10% of all cancers,¹ with an annual incidence of 70-160 per million globally² and 45 per million in South Africa.³ It remains the second most common cause of death in both the United States of America (USA)⁴ and the United Kingdom (UK),⁵ contributing up to 8% of the postneonatal mortality rate worldwide.⁶

Despite improvements in overall survival due to improved supportive care, febrile neutropenia (FN) remains one of the most common complications of chemotherapy.^{7,8}

There is no current evidence-based method to accurately rule out an infectious cause of fever; therefore, FN episodes are managed according to the standard approach of hospital admission and intravenous antibiotics.^{9,10} Recent guidelines recommend the use of a validated scoring system to assess the risk of infectious complications and individualised patient management.⁹

A risk prediction strategy will assist in differentiating patients at high risk of bacteraemia, invasive bacterial infection (IBI) and/or death from low-risk patients in whom the possibility of early step-down to oral antibiotics and outpatient treatment can be considered.¹¹

This prospective study aimed to validate a risk assessment tool published by Ammann et al¹² to distinguish between high-risk and low-risk paediatric oncology patients who might develop adverse events (AEs) during FN at the Tygerberg Paediatric oncology unit. Identification of a low-risk group would enable early step-down from intravenous to oral antibiotics that could benefit the institution financially, with a reduction in discomfort to the patients. A risk stratification would also assist with early recognition of complications through intensive monitoring of high-risk patients.

1.2 Literature review

Childhood cancer represents 1-10% of all cancers globally, with approximately 160 000 new cases diagnosed annually, resulting in approximately 90 000 deaths per annum.¹ According to the International Incidence of Childhood Cancer (Vol. 2), the global age-standardised annual incidence has been estimated to be between 70 and 160 per million in children aged 0 -14 years.² In South Africa, the incidence of childhood cancer has been estimated to be approximately 45 per million.³ Despite its low incidence, childhood cancer remains the second most common cause of death in children aged 5-14 years in both the USA⁴ and the UK,⁵ contributing up to 8% of the global postneonatal mortality rate, according to a report by the World Health Organization (WHO) in 2015.⁶

The five-year overall survival for childhood cancer has been estimated to be as high as 75%, but despite huge improvements in supportive care, close to 16% of deaths within five years of diagnosis are the result of treatment complications.^{7,8} A South African study reported the overall survival rate in two South African units to be 52.1%,¹³ much lower than the up to 80% five-year survival rate in the USA¹⁴ and the UK.¹⁵ This lower survival rate was attributed to the lower survival of black and mixed-race (coloured) children, probably due to poor nutritional status, advanced disease at diagnosis, genetic factors and associated comorbidities (e.g. human immunodeficiency virus [HIV] infection and tuberculosis [TB]).¹³

A study from the UK found that despite a reduction in treatment related-deaths in children with acute lymphoblastic leukaemia (ALL), infections remained the main cause of death.¹⁶ The majority (85%) of febrile episodes had a bacterial origin, but they could also be the result of viral or fungal infections, blood product transfusions, drug reactions or the malignancy itself.⁸

Castagnola et al reported that neutropenia complicated by fever occurred in 34% of their study population in a prospective study.¹⁷ The incidence and rate of febrile complications varied according to the treatment phase, occurring in more than 40% of neutropenia episodes associated with intensive treatment for acute leukaemia or non-Hodgkin lymphoma, or in preparation for haematopoietic stem cell transplantation. Fever of unknown origin was the most common clinical diagnosis (79% of cases), with bacteraemia demonstrated in only 10% of cases.¹⁷

There is no current evidence-based method to accurately rule out an infectious cause of fever; therefore, FN episodes are managed according to the standard approach of hospital admission and intravenous antibiotics.^{9,10}

A risk prediction strategy will assist in differentiating patients at high risk of bacteraemia, IBI and/or death from low-risk patients in whom the possibility of early step-down to oral antibiotics and outpatient treatment can be considered.¹¹

High-risk patients will need a more aggressive treatment approach with intensive monitoring, broad-spectrum intravenous antibiotics and hospitalisation until resolution of fever, neutropenia and signs of infection, in other words, the current standard approach.^{9,10,11} For the low-risk group, however, a less aggressive approach could result in a shortened antimicrobial course, reduced length of hospitalisation and improvement of the patients' quality of life with reduced cost to the institution.^{8,11}

The Multinational Association for Supportive Care in Cancer¹⁸ describes a clinical risk index that identifies adult patients with FN at low risk for complications with a positive predictive value (PPV) of 91%, a specificity of 68% and a sensitivity of 71%. The score includes factors such as a systolic blood pressure of more than 90 mmHg, active chronic obstructive pulmonary disease (COPD), solid tumour as type, previous fungal infection in a patient with a haematological malignancy, dehydration requiring intravenous fluids, clinical setting at onset of fever and age less than 60 years. As the Multinational Association for Supportive Care in Cancer rule does not include children and due to the rare complication of COPD in children, this rule is of very limited applicability in the paediatric age group.¹⁸

A 2010 systematic review and meta-analysis of the performance of risk prediction rules in children and young people with FN assessed 20 studies and 16 different clinical decision rules in 8 388 episodes of FN and concluded that no system was more effective or reliable than any other.⁸ In a 2012 update, despite nine further risk prediction models evaluated, no rule was identified as superior.¹⁹ As part of its findings, this study concluded that undertaking risk stratification 24-48 hours after the onset of the episode led to much better discrimination as many occult infections would have become clinically apparent during this period.¹⁹

In one of the first attempts to identify a clinical decision rule, Rackoff, Gonin, Robinson, Kreissman & Breitfield found that there was an increased risk of bacteraemia with a fever higher than 39 °C and an absolute monocyte count (AMC) of less than $0.1 \times 10^9/L$ at the time of presentation.²⁰

This was the only rule that could be assessed over several datasets in the 2010 systematic

review but was found to lack discriminatory ability.⁸ A similar retrospective study, focusing on clinical decision rules predicting bacteraemia and the need for intensive care unit (ICU) admission from 1990 to 1996, found a bacteraemia rate of 14% and only 11 (0.9%) out of 1 171 FN episodes resulting in ICU admissions.²¹ The lowest frequency of bacteraemia (6.1%) occurred in children with an AMC of more than or equal to $0.155 \times 10^9/\text{L}$ (sensitivity of 94%; specificity of 17%) on admission. None of the patients identified as low risk according to AMC required ICU admission or died. Level of absolute neutrophil count (ANC), absolute phagocyte count (APC), temperature or platelet count could not be associated with a statistically significant decrease in the risk for bacteraemia. Applying the rule of an AMC of more than or equal to $0.1 \times 10^9/\text{L}$ (Rackoff et al²⁰), the researchers demonstrated a bacteraemia rate of 8.7%, significantly higher than the rate of 6.1% for an AMC more than or equal to $0.155 \times 10^9/\text{L}$.²¹

Alexander, Kelly, Hibberd & Parsons (1995) classified patients as low risk if they were outpatients at the time of presentation, had an anticipated duration of neutropenia of less than seven days and had no significant comorbidity.²² The researchers compared the incidence of AEs in the high- and low-risk groups, determining a rate of 4% in the low-risk group versus 41% in the high-risk group.²² Klaassen, Goodman, Pham & Doyle (2000) performed a prospective study (1996-1998) that derived and validated a 'low-risk' prediction rule.²³ During 227 episodes of FN in 140 patients, 13 prediction variables were prospectively collected in 98% of the episodes but only 1 rule could be validated. It was found that patients whose AMC was more than $0.1 \times 10^9/\text{L}$ at the time of presentation had an 8% and a 5% incidence of significant bacterial infection and bacteraemia respectively, versus 25% and 17% in the high-risk group (monocyte count less than $0.1 \times 10^9/\text{L}$).²³ This correlates with the low incidence of bacteraemia found by Baorto, Aquino, Mullen, Buchanan & Debaun²¹ and validated the Rackoff rule.²⁰ In the 136 episodes of FN included in the validation set, the incidence of significant bacterial infection/bacteraemia was 12/5% if the patient was low risk (monocyte count $> 0.1 \times 10^9/\text{L}$) versus 25/22% if the patient was high risk (monocyte count $< 0.1 \times 10^9/\text{L}$). This translated into a 74% sensitivity in predicting a low-risk group, a 46% specificity and a negative predictive value (NPV) of 88%.²³ The researchers could not validate a temperature higher than 39 °C as an independent risk factor.²³

Santolaya et al, in a prospective multicentre study, identified five factors (C-reactive protein [CRP] more than or equal to 90 mg/L, presence of hypotension, presence of leukaemia, platelet count less than or equal to $50\,000/\text{mm}^3$ and recent chemotherapy) to be associated with an increased risk of IBI.²⁴ The researchers' predictive model demonstrated an increasing risk of IBI according to the number of risk factors present at the time of enrolment, and absence of these risk factors was associated with IBI in only 2%. Elevated CRP as the sole variable had a 38% risk of IBI compared with 17% for low platelets and 21% for recent chemotherapy. Children with two or more risk factors had a risk of IBI that surpassed 48%. High fever and low monocyte count did not reach significance in the researchers' multivariate analysis.²⁴

Santolaya et al (1999 to 2000) performed a prospective evaluation of the above five factors, demonstrating a sensitivity of 92%, a specificity of 76%, a PPV of 82% and an NPV of 90%.²⁵ Phillips, Lehrnbecher, Alexander & Sung (2012) et al, however, concluded in their meta-analysis that the rule had been developed and tested in Chile, which might limit its applicability in Europe and North America.¹⁹ In a similar study, Asturias et al could establish no statistical relationship between the above five risk factors, malnutrition and bacteraemia.²⁶ Asturias, Corral & Quezada (2010) did, however, find that increasing CRP values were directly related to the number of days with fever during hospitalisation and with mortality due to infection. Thrombocytopenia also seemed to be related to an increase in the number of days

with fever and prolonged hospitalisation.²⁶

In a multivariate analysis Rondinelli, Ribeiri & de Camargo (2006)²⁷ determined variables that remained as independent predictive risk factors for severe infectious complications (SICs), which include age less than five years, use of a central venous catheter (CVC), temperature more than 38.5 °C, Hb level less than 7 g/dL (in contrast to the Swiss Paediatric Oncology Group [SPOG] 2003 findings), any clinical focus of infection on first examination and absence of upper respiratory tract infection (URTI) as a model for scoring SICs.²⁷ Two validation datasets of the Rondinelli rule demonstrated a sensitivity of 84% and 62%.¹⁹

Paganini et al studied a weighted score, predicting mortality based on the presence of advanced-stage underlying malignant disease, presence of associated comorbidity and presence of bacteraemia.²⁸ The scoring system according to mortality-related risk factors reached a sensitivity of 100% and a specificity of 84.2% during the derivation set, and a sensitivity of 84.2%, a specificity of 83.2% and an NPV of 99.54% for predicting mortality in the validation set.²⁸

Ammann, Hirt, Lüthy & Aebi derived a scoring system predicting severe bacterial infection based on seven variables with a 96% sensitivity, a 26% cross-validated specificity and an NPV of 91% in a retrospective, single-site cohort study over an eight-year period (1993-2001).²⁹ The 7 variables were identified from a total of 39 covariates with possible relevance to severe bacterial infection and that were accessible to the treating physicians within the first 2 hours after fulfilment of the criteria for FN. Weighted factors included bone marrow involvement, no clinical signs of viral infection, high serum CRP levels, leukopenia, presence of a CVC, high Hb levels and a diagnosis of pre-B-cell ALL.²⁹ During the systematic review by Phillips et al, three studies provided data to test this rule with a pooled average sensitivity of 98% but a pooled average specificity of only 13%.¹⁹ The SPOG 2003 trials developed a weighted scoring system for the prediction of bacteraemia at reassessment and identified 4 variables in a subset of 423 FN episodes, which included a Hb level more than or equal to 9 g/dL (weight 3), a platelet count less than 50 g/L (weight 3), shaking chills (weight 5) and another reason for inpatient treatment or observation (weight 3).³⁰ Applying a threshold of more than or equal to three, the score, which was simplified into a low-risk checklist, predicted bacteraemia with 100% sensitivity and 15% specificity. The researchers concluded that predicting bacteraemia at reassessment (at 8-24 hours) was better than the prediction at presentation.³⁰ In assessing factors that would predict future AEs in a different subset of patients included in the SPOG 2003 study population, Ammann et al developed a weighted score with four variables through a multivariate mixed logistic regression model.¹ Using preceding chemotherapy that is more intensive than ALL maintenance treatment (weight = 4), Hb level more than or equal to 9 g/dL (weight = 5), leukocyte count less than 0.3 g/L (weight = 3) and platelet count less than 50 g/L (weight = 3), a score (sum of weights) more than or equal to nine predicted future AEs with an overall sensitivity of 92%, a specificity of 45% and an NPV of 93%. The score's predictive value and sensitivity increased when used at reassessment at 8-24 hours. Of concern, however, was that only one of the three patients who died during the study would have been identified as being at high risk of an AE according to this prediction score.¹²

Miedema et al attempted to validate the Ammann prediction rule¹² in their study population in the Netherlands and demonstrated a sensitivity of only 69% at first presentation and 82% upon reassessment at 8-24 hours.³¹ Applying this prediction rule to their study population, one in three patients with bacteraemia was incorrectly classified as being at low risk of AEs. The

researchers attributed these differences in sensitivity to differences in treatment protocols, microbiological environment, retrospective data collection and genetic factors.³¹

Severe medical complications (SMCs), defined as potentially life-threatening complications, the need for transfer to the paediatric ICU or death, were assessed in another subset of the SPOG 2003 FN study, and it was found that an SMC was reported in 5.6% of 443 FN episodes, identifying 4 characteristics significantly and independently associated, namely diagnosis of acute myeloblastic leukaemia (AML), 7 days or less since last chemotherapy, severely reduced general condition and HB level less than or equal to 90 g/L.³² The group concluded that SMCs were rare in children with FN and mortality was very low. Those with an SMC often had a delayed onset and biphasic clinical course with secondary deterioration.³² In a more recent study from Iran, five variables were identified that, if all present, were associated with a 100% risk of a life-threatening infection.³³ These variables were temperature more than or equal to 39 °C, presence of mucositis, abnormal chest radiograph, platelet count less than 20 000 cells/mm³ and neutrophil count less than 100 cells/mm³.³³

Many studies on the appropriate treatment of FN have been conducted. A Canadian survey (2005) found several modified treatment regimens, varying from traditional inpatient management with antibiotics until neutropenia resolved to alternative regimens in which antibiotics were only continued until the patient was afebrile for 5-7 days.³⁴ In 1 of the subsets of the prospective multicentre SPOG 2003 FN study, patients were found to be low risk according to 10 predefined low-risk criteria, and 6 additional criteria were randomised into an experimental group (stepped down to oral antibiotics within 24 hours) and a control group. The experimental treatment was not shown to be noninferior to the standard treatment (100% vs. 97%), but a limitation was the premature closure because of insufficient patient accrual, resulting in a very small power to detect noninferiority regarding safety.¹¹

Ammann (2004) reviewed available data to support outpatient oral antibiotic use in low-risk episodes of FN and found three single-centre randomised controlled trials comparing oral to intravenous antimicrobial therapy.³⁵ The researchers concluded that although these studies had found no significant differences in mortality and treatment success, they were all underpowered and due to their exclusion criteria could not be applied to the average patient cohort in most paediatric oncology units.³⁵

Several studies assessing biomarkers for their predictive value in FN have been performed. Secmeer et al compared the diagnostic and follow-up value of procalcitonin (PCT) compared to CRP and erythrocyte sedimentation rate (ESR) in documenting infection in patients with FN undergoing intensive chemotherapy and found PCT and CRP levels to be significantly higher in FN patients than in the control group (cancer patients without fever).³⁶ ESR showed no significant difference. In sequential analyses of patients without documented infections, the median of PCT concentrations showed a tendency to decrease after 8 hours after the onset of fever, whereas in patients with documented infection, it only decreased after 48 hours. The researchers also found that the PCT concentrations remained the same over the entire period in patients with prolonged fever (more than 72 hours).

They concluded that PCT was a more sensitive marker for early detection of bacterial infection, especially taking into consideration the slow rise in CRP levels.³⁶ Miedema et al concluded that interleukin (IL)-8 was the most useful marker for the early detection of bacterial infections but because it is influenced by the presence of gastrointestinal mucositis (in contrast to PCT levels that are not affected), PCT might be more useful.³⁷ IL-8 used in combination with clinical parameters or PCT reached 100% sensitivity in identifying bacterial infection. With sequential

testing after 24-48 hours, only PCT remained elevated in bacterial infections, while IL-8 remained significantly increased during mucositis.³⁷ Kitanovski, Jazbec, Hojker, Gubina & Dergane (2006) reported that IL-6 and PCT were more sensitive and specific as early markers of bacteraemia/clinical sepsis than CRP in children with FN and that sequential PCT determinations improved its diagnostic accuracy.³⁸ Mian et al divided patients with FN into a high-risk and a low-risk group according to predefined criteria (prolonged hospitalisation for 7 or more days, admission to a paediatric ICU or a confirmed bacteraemia) to analyse the 18 serum biomarkers, including CRP, PCT and ILs.³⁹ Upon presentation, a PCT level > 0.11 mg/ml had a 97% sensitivity to predict high risk for FN, while a CRP level of > 100 mg/L had a sensitivity of 88%.³⁹

Based on the literature presented above, it becomes apparent that although many researchers have undertaken the task of identifying an accurate prediction rule, few rules have been successfully validated. Identification of a low-risk group would enable early step-down from intravenous to oral antibiotics that would financially benefit the institution, with a reduction in discomfort to the patients. A risk stratification would also assist with early recognition of complications through intensive monitoring of high-risk patients. As already mentioned, Ammann developed a risk prediction model during the SPOG 2003 trials.¹² Using basic information on chemotherapy and blood tests available shortly after admission, they predicted AEs with a 92% sensitivity. Using the same outcomes and definitions in my study, we aimed to validate the sensitivity, specificity, PPV and NPV of the Ammann rule in our patient population.

CHAPTER 2: RESEARCH DESIGN AND METHODOLOGY

2.1 Purpose of the study

The purpose of the study was to validate an existing clinical risk assessment tool (Ammann tool¹²) to predict AEs in children with cancer and FN, using four variables, including Hb level, total WCC, platelet count and phase of chemotherapy, to distinguish between high-risk and low-risk paediatric oncology patients who might develop AEs during FN.

2.2 Objectives

2.2.1 Primary objective

The primary objective was to validate the sensitivity, specificity, PPV and NPV of the clinical risk assessment tool (Ammann tool¹) in our study population.

2.2.2 Secondary objectives

- Identification of risk factors that could predict a group of patients at high risk of an AE during FN.
- Identification of factors predicting a low-risk patient group with no AEs during FN.
- Identification of additional factors associated with an AE.
- Identification of the current micro-organism profile and sensitivities with subsequent review of the current antibiotic protocol use.
- Cross-validation of other predefined risk prediction tools including the rules derived by Rondinelli,³² Santolaya,³⁰ Rackoff¹⁹ and Baorto.²⁰

2.3 Methodology

This was a prospective study, and enrolment was from 22 January 2014 to 22 January 2016 in the paediatric oncology unit at Tygerberg Hospital, Cape Town, South Africa. Patients aged 0-15 years receiving chemotherapy and who presented with fever or a history of fever were enrolled in the study. Informed consent was obtained from the parents/guardians (appendixes A, B and C) and assent from all children older than seven years (appendixes D, E and F). Telephonic verbal consent was accepted in cases where parents/guardians were not present at the time of enrolment or children were too ill to write.

2.3.1 Inclusion criteria

- All patients 0-15 years of age at time of presentation.
- Fever as defined below or history of a fever before presentation.
- Confirmed neutrophil count ≤ 500 cells/mm³.
- All patients with a confirmed malignancy.
- All patients presenting with FN between 22 January 2014 and 22 January 2016.

2.3.2 Exclusion criteria

- Patients older than 16 years.
- Patients without a fever or history of a fever.
- Patients with a neutrophil count > 500 cells/mm³.
- Patients presenting beyond the study time period.
- Patients without a known or confirmed malignancy.

2.4 Data collection

The data collected on each patient included the following:

- Patient-related parameters
 - Age
 - Gender
 - Vital signs: temperature, pulse rate, respiratory rate and blood pressure
 - Nutritional status (weight and length/height)
 - Clinical focus of infection
 - Presence of comorbidities
- Disease-related parameters
 - Presence of a CVC
 - Type of CVC
 - Type of malignancy
 - Chemotherapy regimen
 - Phase of chemotherapy
 - Number of days since last chemotherapy
- Biomarkers
 - Hb
 - Leukocyte count
 - ANC
 - AMC
 - Platelet count
 - CRP
 - PCT
 - Blood culture result and sensitivity profile
 - Chest radiograph if performed
 - Other culture results

Routine blood samples, including blood cultures, full blood count, differential WCC, CRP and PCT, were collected by the admitting physician. Blood cultures were obtained from peripheral venous or arterial sites and/or CVCs (according to National Health Laboratory Service guidelines – Appendix H). Based on the patient's clinical condition and according to the discretion of the attending/admitting physician, other cultures and radiological investigations were performed.

All patients were treated and monitored according to the current standard of care hospital protocol (Appendix I) with empiric broad-spectrum intravenous antibiotics (piperacillin-tazobactam and amikacin).⁴⁰ In cases where fever persisted beyond 48 hours despite treatment according to the hospital protocol, cultures and other appropriate tests were repeated and additional antibacterial (Vancomycin for Methicillin-resistant *Staphylococcus aureus*) and/or antifungal cover (Fluconazole) was added. All patients were evaluated daily by the attending

oncology team. Patients were followed up for the development of AEs until seven days after antimicrobial treatment had stopped or severe neutropenia had resolved while they were managed as inpatients. An episode was considered to have resolved once the neutrophil count had recovered to above 500 cells/mm³ or the patient was no longer acutely ill. More than one episode of FN per patient were enrolled.

All chest radiographs were reported by an expert single paediatric pulmonologist.^{41,42} Chest radiographs were reported in clinical context with specific reference to type of radiographic change in the presence or absence of any clinical symptoms of a lower respiratory tract infection (LRTI). Identifying an underlying cause for abnormal radiographic changes was beyond the scope of this study.

2.5 Definitions

The following definitions were used at enrolment:

- Fever: An axillary temperature ≥ 38.0 °C on two occasions over a 24-hour period or ≥ 38.5 °C once.
- Neutropenia: An ANC ≤ 500 cells/mm³.
- CVC: Broviac catheter or external venous port.
- Body mass index (BMI) classification according to the WHO.⁴³
 - Severe wasting – BMI below the -3 Z-line.
 - Wasting – BMI between the -3 and -2 Z-lines.
 - Normal – BMI between the -2 and +1 Z-lines.
 - At risk of overweight – BMI between the +1 and +2 Z-lines.
 - Overweight – BMI between the +2 and +3 Z-lines.
 - Obese – BMI above the +3 Z-line.
- Common Terminology Criteria for Adverse Events.⁴⁴
 - Hb:
 - Grade 1: Hb >10 g/dL
 - Grade 2: Hb 8-10 g/dL
 - Grade 3: Hb < 8 g/dL
 - Grade 4: life threatening
 - WCC:
 - Grade 1: $> 3.0 \times 10^9/L$
 - Grade 2: $2.0-3.0 \times 10^9/L$
 - Grade 3: $1.0-2.0 \times 10^9/L$
 - Grade 4: $< 1.0 \times 10^9/L$
 - Platelets:
 - Grade 1: $> 75.0 \times 10^9/L$
 - Grade 2: $50.0-75.0 \times 10^9/L$
 - Grade 3: $25.0-50.0 \times 10^9/L$
 - Grade 4: $< 25.0 \times 10^9/L$
- AE: SMC as a result of infection, microbiologically defined infection (MDI) and radiologically confirmed pneumonia (RCP).
 - SMC: Death, complication requiring ICU treatment and potentially life-threatening complication as judged by the treating physician.

- MDI: Positive bacterial or fungal culture from a normally sterile body fluid compartment and detection of a viral antigen or product of polymerase chain reaction by a validated microbiologic method.
- RCP: The presence of clinical symptoms and radiographic changes suggestive of an LRTI.

2.6 Statistical analysis

A statistician from Stellenbosch University was consulted to assist with data analysis. Microsoft Excel was used to capture individual episodes as well as the collective data.

One-way analysis of variance (ANOVA) was used to test for differences in means of continuous measurements between the AEs and no-events groups. The usual assumptions of ANOVA were checked at all times and were found to be satisfactory. Summary statistics were reported as means and standard deviations. Sensitivity, specificity, PPV and NPV were calculated from cross-tabulations between the AEs groups and the scoring regime groupings. A significance level of 5% ($p < 0.05$) was used as guideline for determining significant differences.

2.7 Ethical considerations

Ethics approval was obtained from the Health Research Ethics Committee at Stellenbosch University on 22 January 2014. Research was subsequently conducted in accordance with internationally accepted ethical standards and guidelines. Each potential study participant and his/her parents/guardians were counselled in their first language or language of choice regarding the purpose, advantages and risks of participation in the study. In cases where the patients' or parents/guardians' first language was Xhosa, an interpreter was used to explain this information. All parents/guardians and participants were provided with an information leaflet in their first language (Appendix A, B, C). Informed consent (appendix D, E, F) was obtained from parents/guardians and assent from children older than seven years.

Confidentiality was maintained by assigning a unique study number to each patient data set, specifying the episode number, patient number and episode per specific patient. This list was kept separate from the original data set. Data analysis was done anonymously using unique study numbers with no identifiable data present at analysis.

CHAPTER 3: RESULTS

3.1 Epidemiology and overall description of episodes of febrile neutropenia

Within the 2-year study period, a total of a 100 episodes of FN were reported in 52 patients with a median of 2 episodes per patient (range of 1 to 5). No episodes were excluded as strict inclusion criteria were followed and all patients approached for enrolment consented to participation. Of these, 67% of episodes occurred within seven days of completing chemotherapy. Median patient age for all episodes was 56 months (mean age 71 months; range 8 to 175 months). The male:female ratio was 1.8:1. There were more patients in the second year of data collection with an 18% increase in FN episodes compared to the first year, with no clear seasonal predilection (Figure 3.1). This increase was probably due to the increased number of newly diagnosed children with malignancies in 2015 (n = 73) versus 2014 (n = 56).

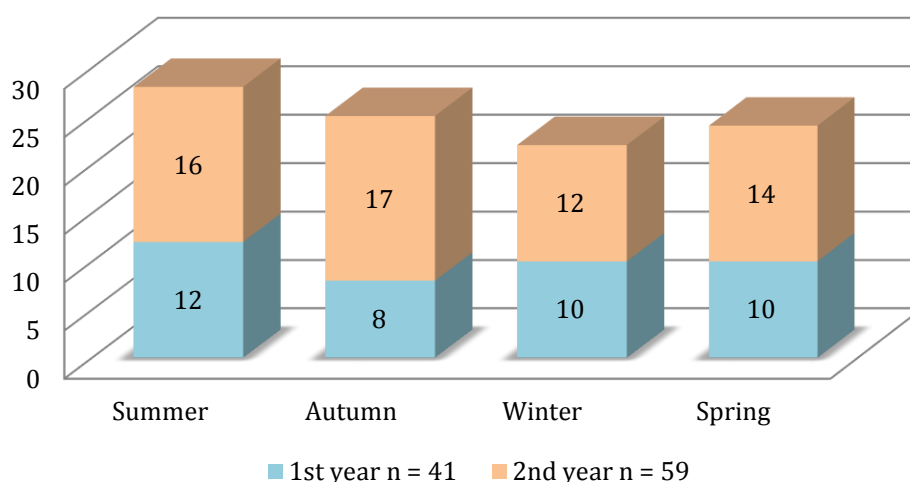


Figure 3.1: Annual and seasonal distribution of febrile neutropenia episodes

Summer: December to February, Autumn: March to May, Winter: June to August, Spring: September to November

The study population included 28 haematological malignancies and 24 solid tumours, with respectively 54% and 46% of FN episodes (16% in relapse malignancies) (Figure 3.2). ALL was the most common malignancy (15 patients, 28% FN episodes) followed by acute myeloblastic leukaemia (AML) in 8 patients (24% FN episodes) and lymphoma in 4 patients (5% FN episodes).

The 22 patients with solid tumours included 4 patients with rhabdomyosarcoma (6% FN episodes), 4 patients with Ewing sarcoma (6% FN episodes), 3 patients with retinoblastoma (8% FN episodes), 3 patients with nephroblastoma (7% FN episodes), 3 patients with osteosarcoma (3% FN episodes) and 3 patients with neuroblastoma (7% of FN episodes). Only 2 patients (2% of FN episodes) had central nervous system (CNS) tumours (1 patient with an astrocytoma and 1 patient with a supracellar choriocarcinoma).

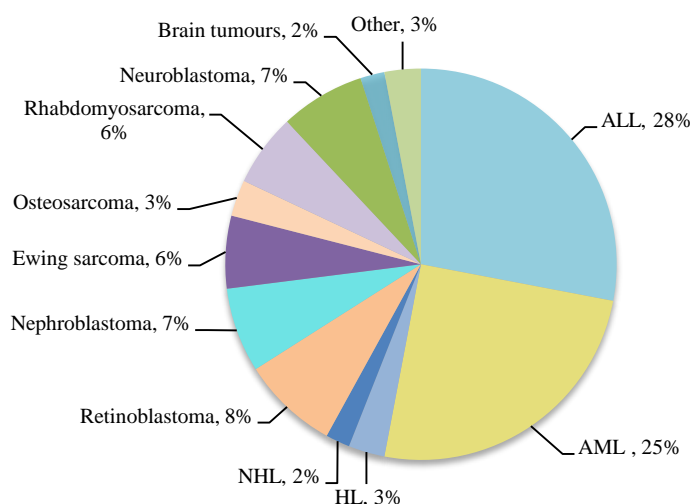


Figure 3.2: Febrile neutropenia episodes (n = 100)

ALL – acute lymphoblastic leukaemia, AML – acute myeloblastic leukaemia, HL – Hodgkin’s lymphoma, NHL – non-Hodgkin lymphoma

Twenty-four percent of FN episodes occurred in patients with solid tumours with advanced disease: six episodes in a patient with Stage 4 retinoblastoma, three episodes in a patient with Stage 4 neuroblastoma, two episodes in two patients with Stage 4 osteosarcoma, two episodes in a patient with Stage 3 rhabdomyosarcoma, four episodes in three patients with Stage 4 rhabdomyosarcoma, six episodes in two patients with Stage 4 neuroblastoma and one episode in one patient with Stage 3 neuroblastoma.

In 24 of the 100 FN episodes (24%), a CVC was in situ, including 9 internal venous ports, 14 external Broviac lines and 1 temporary CVC.

3.2 Comorbidities

Comorbidities were associated with 18% of the febrile episodes and included trisomy 21 in three patients (two AML and one pre-B-cell ALL), drug-induced dilated cardiomyopathy (DCMO) in two patients (nephroblastoma and Ewing sarcoma), one patient each with primary variable immunodeficiency (B-cell lymphoma), malignancy-associated hypertension (neuroblastoma), drug-induced tubulopathy (T-cell ALL), femoral deep vein thrombosis (pre-B-cell ALL), HIV (Kaposi sarcoma) and pulmonary TB (osteosarcoma) and a patient with vancomycin-resistant enterococcus (VRE) gastrointestinal colonisation (AML) (Table 3.1).

Table 3.1: Comorbidities

| Comorbidity | Malignancy | No of FN episodes | AE |
|-----------------------------------|----------------|-------------------|----------|
| Trisomy 21 | AML | 3 | 1 |
| Trisomy 21 | AML | 1 | 1 |
| Trisomy 21 | Pre-B-cell ALL | 2 | 1 |
| DCMO | Nephroblastoma | 2 | 1 |
| DCMO | Ewing sarcoma | 1 | None |
| Primary variable immunodeficiency | B-cell ALL | 1 | 1 |
| Hypertension | Neuroblastoma | 2 | 1 |
| Drug-induced tubulopathy | T-cell ALL | 1 | None |
| Pulmonary TB | Osteosarcoma | 1 | None |
| HIV | Kaposi sarcoma | 1 | None |
| Femoral DVT | Pre-B-cell ALL | 1 | None |
| VRE colonisation | AML | 2 | 1 |
| Total | | 18 | 7 |

AML – acute myeloblastic leukaemia, ALL – acute lymphoblastic leukaemia, DCMO – dilated cardiomyopathy, TB – tuberculosis, HIV – human immunodeficiency virus, DVT – deep vein thrombosis, VRE – vancomycin resistant colonization

3.3 Clinical site of infection

The FN episodes were classified (Table 3.2) as fever of unknown origin in 37% of episodes with one or more identifiable infectious focus in 63% of episodes. The most common clinical demonstrable site of infection was mucositis (15%) followed by acute gastroenteritis/typhlitis (12%) and URTI (11%).

Table 3.2: Clinical site of infection with associated adverse event type

| Clinical site | Outcome | | | Type of adverse event | | |
|-----------------------------------|-----------|---------|------------|-----------------------|-----|-----|
| | Total | With AE | Without AE | MDI | SMC | RCP |
| Fever of unknown origin | 37 | 10 | 27 | 8 | 2 | 2 |
| URTI | 11 | 3 | 8 | 2 | 1 | 0 |
| LRTI | 4 | 3 | 1 | 1 | 1 | 3 |
| AGE/typhlitis | 12 | 2 | 10 | 1 | 1 | 1 |
| Mucositis | 15 | 6 | 9 | 6 | 1 | 0 |
| Skin/soft tissue infection | 4 | 3 | 1 | 2 | 1 | 1 |
| CVC-related infection | 3 | 2 | 1 | 2 | - | - |
| UTI | 3 | 3 | 0 | 3 | - | - |
| Other | 5 | 3 | 2 | 3 | - | - |
| ≥ 1 site of infection | 6 | 4 | 2 | 2 | 1 | 3 |

URTI – upper respiratory tract infection, LRTI – lower respiratory tract infection, AGE – acute gastroenteritis, CVC – central venous catheter, UTI – urinary tract infection, AE – adverse event, MDI – microbiologically defined infection, SMC – severe medical complication, RCP – radiologically confirmed pneumonia

3.4 Adverse events

In 40 of the 100 episodes of FN, 1 or more AE occurred, including 33 MDIs, 10 RCPs and 9 SMCs (Figure 3.3). AEs occurred in 3 of the 4 skin/soft tissue infections, 2 of the 3 CVC-related infections and 10 of the 37 episodes with a fever of unknown origin. In the 3 cases of clinical urinary tract infection, an organism was isolated. More than 1 site of infection was found in 6 episodes, associated with 4 AEs (Table 3.2). Only 12 of these episodes were associated with a CVC, including 2 episodes that presented with a clinically infected CVC site.

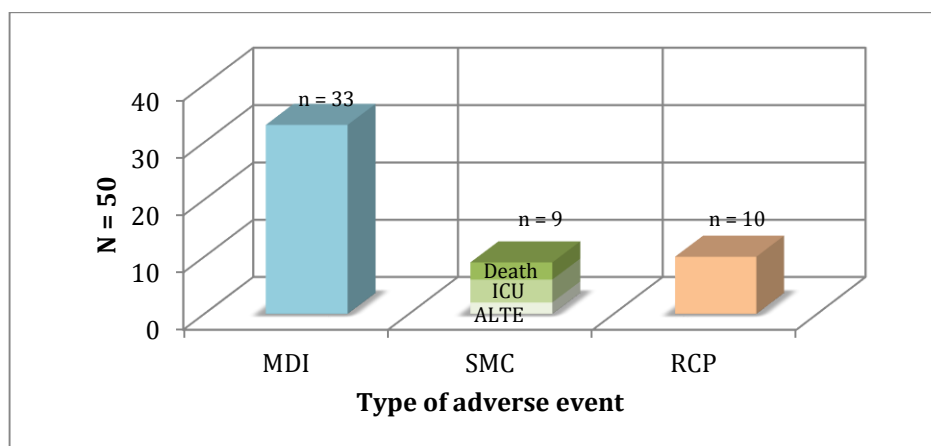


Figure 3.3: Type of adverse event (≥ 1 adverse event/episode)

MDI – microbiologically defined infection, SMC – severe medical complication, ALTE – acute life-threatening event, RCP – radiologically confirmed pneumonia

Chest radiographs were performed in 32 of the 100 episodes based on the presence of clinical features suggestive of an LRTI or in episodes of fever of unknown origin. Despite 10 RCPs documented as AEs, clinical symptoms suggestive of an LRTI were only present in 4 patients on presentation with FN. Of the remaining 22 chest radiographs, only 3 were reported as normal with abnormalities in the lung fields noted in the rest. The abnormalities were classified as lobar opacification on nine radiographs, interstitial infiltrates on six radiographs and bronchopneumonic changes on three radiographs.

The SMCs (Table 3.3) included two life-threatening events with four ICU admissions and three deaths. The three deaths included two patients classified as high risk and one patient classified as low risk. One patient with Stage 2 nephroblastoma with an Ammann score of 9 (high risk) died from septic shock due to *Streptococcus mitis/oralis*. The second high-risk patient with an Ammann score of 12 (high risk) died of lobar pneumonia associated with septic shock during the induction phase of AML. The low-risk patient, with an Ammann score of 7, died during the intensification phase of treatment for relapsed pre-B-cell ALL after developing gastroenteritis, multilobar pneumonia and septic shock. *Pseudomonas aeruginosa* was isolated from a tracheal aspirate done after intubation of this patient.

Table 3.3: Overview of severe medical complications

| Age (months) | Sex | Malignancy | Risk | Clinical focus of infection | Comorbidity | Course |
|----------------------|-----|------------------------------------|------|-----------------------------|--------------|---|
| Death | | | | | | |
| 78 | F | Nephroblastoma Stage 3 | High | Tonsillitis | None | Refractory septic shock, <i>S. mitis/oralis</i> bacteraemia |
| 29 | F | AML | High | None | T21, ASD | Persistent neutropenia, pneumonia complicated by hypoxaemia (cardiovascular collapse with endotracheal intubation) |
| 54 | M | Pre-B-cell ALL, relapse | Low | AGE, mucositis | None | ICU admission, refractory septic shock, pneumonia complicated by hypoxaemia, <i>P. aeruginosa</i> on tracheal aspirate |
| ICU admission | | | | | | |
| 22 | M | Astrocytoma | High | Croup | None | UAO, candidal esophagitis and tracheitis, septic shock, refractory hypotension (inotropic support) |
| 32 | M | ALL | High | None | None | Septic shock, refractory hypotension (inotropic support), <i>Staphylococcus aureus</i> bacteraemia |
| 32 | F | Neuroblastoma Stage 4 | High | None | Hypertension | Soft tissue abscess eight days post admission, <i>Escherichia coli</i> bacteraemia, hypoxic RCP |
| 158 | M | Metastatic retinoblastoma, relapse | High | Cellulitis | None | Septic shock, refractory hypotension (inotropic support), polymicrobial bacteraemia (<i>E. coli</i> (2 strains), <i>S. aureus</i>), pneumonia complicated by hypoxaemia |
| ALTE | | | | | | |
| 29 | M | APL | Low | AGE | None | Pneumonia complicated by hypoxaemia, chronic gastroenteritis, severe hypokalaemia |
| 134 | M | AML | High | AGE, mucositis | None | Upper gastrointestinal bleed, hypovolemic shock |

F – female, M – male, T21 – trisomy 21, ASD – atrial septal defect, APL – acute promyelocytic leukaemia, AGE – acute gastroenteritis, ALTE – acute life-threatening event, UAO – upper airway obstruction, ICU – intensive care unit

3.5 Pathogens identified

Pathogens were isolated in 24 bacteraemias (including 4 polymicrobial bacteraemias), 3 respiratory tract infections, 4 urinary tract infections and 2 positive skin/wound puss swabs (including 1 from a Broviac site). Importantly, in six of the nine ALTEs (including all four ICU admissions and two deaths), organisms were isolated from an otherwise sterile bodily fluid. The majority (58%; n = 18) were Gram-positive bacteraemias with 5 (13%) *S. aureus* (including 2 methicillin-resistant *S. aureus* species), 9 (23%) *Streptococcus* species and 3 *Enterococcus* species. Gram-negative bacteraemia was detected in 41% (n = 13) episodes, including 3 (9%) *Klebsiella pneumoniae*, 4 (11%) extended-spectrum beta-lactamase-producing *K. pneumoniae* and 6 (15%) *E. coli* isolates. *Candida albicans* was isolated from a tracheal aspirate in one FN episode that was associated with an ALTE and ICU admission. The microbiological organism profile and site of recovery are demonstrated in Table 3.4.

Table 3.4: Bacterial/fungal species recovered for 100 episodes of febrile neutropenia among children with microbiologically defined infections according to site of the isolate

| <u>No. of isolates by site of recovery</u> Isolate | Blood | CVC | Urine | Airway secretions | Pus swab | Total |
|---|-------|-----|-------|-------------------|----------|-------|
| <i>Staphylococcus aureus</i> | 3 | - | - | - | 1 | 4 |
| Methicillin-resistant <i>Staphylococcus aureus</i> | 1 | - | - | - | 1 | 2 |
| <i>Staphylococcus epidermidis</i> | - | 1 | - | - | - | 1 |
| <i>Streptococcus salivarius</i> | 2 | - | - | - | - | 2 |
| <i>Streptococcus oralis/mitis</i> | 4 | - | - | - | - | 4 |
| <i>Streptococcus vestibularis</i> | 1 | - | - | - | - | 1 |
| <i>Streptococcus sanguis</i> | 1 | - | - | - | - | 1 |
| Group A beta-haemolytic <i>Streptococcus</i> | 1 | - | - | - | - | 1 |
| <i>Enterococcus faecium</i> | - | - | 2 | - | - | 2 |
| <i>Enterococcus cloacae</i> | 1 | - | - | - | - | 1 |
| <i>Escherichia coli</i> | 5 | - | 1 | - | - | 6 |
| <i>Pseudomonas aeruginosa</i> | 2 | - | - | 1 | - | 3 |
| <i>Klebsiella pneumoniae</i> | 3 | - | - | - | - | 3 |
| ESBL <i>Klebsiella pneumoniae</i> | 3 | - | - | 1 | - | 4 |
| <i>Proteus mirabilis</i> | - | - | 1 | - | - | 1 |
| <i>Klebsiella oxytoca</i> | 1 | - | - | - | - | 1 |
| <i>Candida albicans</i> | - | - | - | 1 | - | 1 |
| <i>Neisseria sicca</i> | 1 | - | - | - | - | 1 |
| Totals | 29 | 1 | 4 | 3 | 2 | 39 |

CVC – central venous catheter, ESBL – extended-spectrum beta-lactamases producing

3.6 Bacterial sensitivity and resistance patterns

As part of the organism profile, we also assessed the bacterial sensitivity and resistance patterns (Table 3.5) to assess the feasibility of an oral protocol and the efficacy of the current antibiotic protocol in use. Although the number of organisms isolated was too few to demonstrate any statistically significant pattern, it became apparent that predominantly Gram-positive organisms were isolated (58%). Our current empiric antibiotic protocol includes piperacillin-tazobactam and amikacin as first-line treatment. Based on the sensitivity testing, 3 (8%) out of 39 organisms were resistant to piperacillin-tazobactam, including 1 *E. coli* (3%) and 2 *P. aeruginosa* (5%) isolates. The same two *P. aeruginosa* isolates were also resistant to amikacin. Of concern, however, is the fact that the Gram-negative organisms showed extensive resistance to most of the standard first-line intravenous antibiotics.

Table 3.5: Micro-organism sensitivity and resistance patterns

| Antibiotic | | Gram positive (n=19) | | | | | | | Gram negative (n=19) | | | | | | |
|----------------|--------------|-------------------------|-----------|-----|-----------|-----|--------------|----|-------------------------|-----------|-----|-----------|------|--------------|------|
| | | No. of organisms tested | Sensitive | | Resistant | | Intermediate | | No. of organisms tested | Sensitive | | Resistant | | Intermediate | |
| | | | No. | % | No. | % | No. | % | | No. | % | No. | % | No. | % |
| Beta-lactams | Penicillin | 15 | 5 | 33 | 8 | 54 | 2 | 13 | 1 | 1 | 100 | | | | |
| | Ampicillin | 11 | 4 | 36 | 2 | 46 | 2 | 18 | 15 | 1 | 7 | 14 | 93 | | |
| | Augmentin | 1 | | | 1 | 100 | | | 10 | 4 | 40 | 5 | 50 | 1 | 10 |
| | Cloxacillin | 7 | 4 | 57 | 3 | 43 | | | | | | | | | |
| Cephalosporins | Cefuroxime | 2 | 1 | 50 | | | | | 12 | 8 | 67 | 4 | 33 | | |
| | Ceftazidime | | | | | | | | 8 | 4 | 50 | 3 | 38 | 1 | 12 |
| | Cefotaxime | 8 | 7 | 88 | 1 | 12 | | | 13 | 10 | 77 | 3 | 33 | | |
| | Ceftriazone | 6 | 5 | 83 | 1 | 17 | | | 11 | 8 | 73 | 3 | 27 | | |
| | Cefipime | | | | | | | | 6 | 2 | 33 | 3 | 50 | 1 | 17 |
| ML | Erythromycin | 13 | 9 | 69 | 4 | 31 | | | | | | | | | |
| | Clindamycin | 12 | 9 | 75 | 3 | 25 | | | | | | | | | |
| | Tobramycin | | | | | | | | 1 | | | 1 | 100 | | |
| CP | Ertapenem | 1 | 1 | 100 | | | | | 6 | 6 | 100 | | | | |
| | Meropenem | | | | | | | | 8 | 8 | 100 | | | | |
| | Imipenem | | | | | | | | 8 | 7 | 88 | 1 | 12 | | |
| AGC | Gentamycin | 4 | | | 3 | 100 | | | 14 | 9 | 64 | 5 | 34 | | |
| | Amikacin | | | | | | | | 8 | 6 | 75 | 1 | 12.5 | 1 | 12.5 |

| | | | | | | | | | | | | | | | |
|-------|---------------|-------------------------|-----------|-----|-----------|----|--------------|---|-------------------------|-----------|-----|-----------|----|--------------|---|
| Q | Ciprofloxacin | 3 | 3 | 100 | | | | | 13 | 9 | 69 | 3 | 23 | 1 | 8 |
| Other | Pip-Taz | | | | | | | | 5 | 3 | 60 | 2 | 40 | | |
| | Bactrim | 8 | 6 | 75 | 2 | 25 | | | 13 | 4 | 31 | 9 | 69 | | |
| | Antibiotic | Gram positive (n=19) | | | | | | | Gram negative (n=19) | | | | | | |
| | | No. of organisms tested | Sensitive | | Resistant | | Intermediate | | No. of organisms tested | Sensitive | | Resistant | | Intermediate | |
| | | | No. | % | No. | % | No. | % | | No. | % | No. | % | No. | % |
| | Rifampicin | 4 | 2 | 50 | 2 | 50 | | | | | | | | | |
| | Vancomycin | 8 | 7 | 88 | 1 | 12 | | | | | | | | | |
| | Colistin | | | | | | | | 2 | 2 | 100 | | | | |
| | Linezolid | 2 | 2 | 100 | | | | | | | | | | | |
| | Fucidic acid | 2 | 1 | 50 | 1 | 50 | | | | | | | | | |

ML – Macrolides, CP – Carbapenems, AGC – Aminoglycosides, Q – Quinolones.

3.7 Categorisation of weight distribution

The majority (65%) of episodes (30 patients) in both the high- (26%) and low- (39%) risk groups were in patients with a normal BMI, and 25 of the AEs occurred in this group, including all 3 deaths (Table 3.6). Eight AEs occurred in 11 episodes of 6 patients who were severely wasted, 2 AEs occurred in 7 episodes of 4 patients who were wasted, 3 AEs occurred in 10 episodes of 5 patients who were at risk for overweight, 1 AE occurred in each of 2 overweight patients and 1 AE occurred in each of 2 obese patients.

Table 3.6: Weight distribution with associated risk category and outcome (%)

| | Total | High risk | Low risk | AE | MDI | SMC | RCP |
|-----------------------|-------|-----------|----------|----|-----|--------------|-----|
| Severely wasted | 11 | 5 | 6 | 8 | 6 | - | 2 |
| Wasted | 7 | 2 | 5 | 2 | 2 | - | - |
| Normal | 65 | 26 | 39 | 25 | 21 | 6 (3 deaths) | 7 |
| At risk of overweight | 10 | 4 | 6 | 3 | 3 | - | - |
| Overweight | 2 | 1 | 1 | 1 | - | - | 1 |
| Obese | 2 | 1 | 1 | 1 | 1 | 1 | - |

| | | | | | | | |
|----------------|----------|----------|----------|----------|----------|----------|----------|
| Unknown | 3 | 1 | 2 | 2 | 1 | 1 | - |
|----------------|----------|----------|----------|----------|----------|----------|----------|

AE – adverse event, MDI – microbiologically defined infection, SMC – severe medical complication, RCP – radiologically confirmed pneumonia

3.8 C-reactive protein

For 91 episodes, the mean CRP was 118 mg/L (range of < 4 mg/L to 321.9 mg/L) while the CRP was not known in 9 episodes (4 of them associated with an AE). The mean CRP in the patients who suffered an AE, however, did not differ significantly ($p = 0.42$) from that of the patients with no AEs, with a mean CRP of 128 mg/L and 112 mg/L respectively. Only six episodes had a CRP of < 10 mg/L associated with three AEs. The mean CRP in the group with SMCs was higher at 194 mg/L as opposed to the mean of 118 mg/L and 162 mg/L in the groups with MDI and RCP, respectively, which was statistically significant ($p = 0.02$). There was no statistically significant difference in CRP value between the high- and low-risk groups according to the Ammann rule ($p = 0.21$).

3.9 Haematological toxicity grading

The haematological grading of chemotherapy toxicity⁴⁴ (Table 3.7) showed a 75% Grade 4 toxicity for total WCC, a 53% Grade 3 toxicity for Hb and a 35% Grade 4 toxicity for platelets. The mean WCC was $0.83 \times 10^9/\text{L}$ for all episodes and $0.53 \times 10^9/\text{L}$ in episodes with an associated AE. The mean Hb for all episodes was 8.1 g/dL and 8.2 g/dL in episodes with a reported AE. The mean AMC was $0.17 \times 10^9/\text{L}$ compared to $0.08 \times 10^9/\text{L}$ in episodes associated with an AE. The AMC could not be measured in two episodes due to the total WCC being too low.

Table 3.7: Haematological grade of toxicity according to the Common Terminology Criteria for Adverse Events and parameters⁴⁴

| | <u>Toxicity grade</u> | | | | | | | |
|---|-----------------------|-----|-----|------|---------------------|-----------------------------------|--------------------------|-------------------|
| | 1 | 2 | 3 | 4 | Range: all episodes | Interquartile range: all episodes | Mean value: all episodes | Mean value for AE |
| Hb (g/dL) | 19% | 28% | 53% | - | 4.4-18.2 | 6.6-9.4 | 8.1 | 8.2 |
| WCC ($\times 10^9/L$) | 3% | 12% | 10% | 75% | 0.04-5.25 | 0.23-0.99 | 0.83 | 0.53 |
| ANC ($\times 10^9/L$) | | | | 100% | 0.0-0.5 | 0.04-0.16 | 0.07 | |
| AMC ($\times 10^9/L$) | | | | | 0.0-2.08 | 0.01-0.16 | 0.17 | 0.08 |
| Plt ($\times 10^9/L$) | 38% | 9% | 18% | 35% | 3-453 | 15-122 | 81 | 61 |

Hb – haemoglobin, WCC – white cell count, ANC – absolute neutrophil count, AMC – absolute monocyte count, Plt – platelets, AE – adverse event.

3.10 Individual variables

Assessment of the predictive value of individual variables for an AE (Table 3.8) showed that only total WCC and AMC achieved statistical significance with a respective p-value of < 0.01 and 0.05, with univariate analysis. Other variables assessed included age (p = 0.18), BMI (p = 0.64), sex (p = 0.77), temperature (p = 0.69), Hb (p = 0.7), platelets (p = 0.08) and CRP (p = 0.42). With multivariate analysis only BMI (p = 0.03) and Temperature (p = 0.02) achieved statistical significance.

Table 3.8: Performance of individual variables in predicting adverse events

| | AE group (n) | Non-AE group (n) | p-value |
|--|---------------------|-------------------------|------------------|
| Age (months) - mean | 63 | 76 | 0.18 |
| BMI (SD) - mean | 1.8 | 1.9 | 0.64 |
| Sex (male) | 31 | 45 | 0.77 |
| Temperature (°C) - mean | 38 | 37.8 | 0.69 |
| WCC ($\times 10^9/L$) - mean | 0.53 | 1.02 | < 0.01 |

| | | | |
|--|------|------|-------------|
| AMC ($\times 10^9/L$) - mean (excluding 2 episodes with unknown AMC) | 0.08 | 0.23 | 0.05 |
| Hb (g/dL) - mean | 8.2 | 8.0 | 0.7 |
| Platelets ($\times 10^9/L$) - mean | 61 | 94 | 0.08 |
| CRP (mg/L) | 128 | 112 | 0.42 |

AE – adverse event, BMI – body mass index, WCC – white cell count, AMC – absolute monocyte count, Hb – haemoglobin, CRP – C-reactive protein

3.11 Validation of the Ammann tool

By applying the Ammann tool¹² to our study population, 43% of episodes were classified as high risk with 22 AEs occurring in this group, including 2 deaths. The other 18 AEs occurred in the 57% of patients assessed as being at a low risk of suffering an AE and included 1 of the 3 deaths. Applying the calculation used in both the other cohorts the rule achieved a sensitivity of 56.8% (95% CI 39.5% – 72.9%), specificity of 65% (95% CI 51.6% - 76.9%), PPV 50% (95% CI 34.2% - 65.8%) and a NPV of 70.9% (95% CI 34.2% - 65.8%) at reassessment (3 AEs known). Because we were interested in applying the tool at presentation to plan future management we also calculated sensitivity, specificity, PPV and NPV at presentation. Applying the tool at presentation yielded a sensitivity of 55% and a specificity of 65% with a PPV of 51% and the NPV in our cohort of 68% (again no correlation with both Ammann et al¹² and Miedema et al³¹) (Table 3.9).

Table 3.9: Performance of the Ammann rule applied to the three different cohorts

| | Our cohort | | Ammann et al ¹² | Miedema et al ³¹ | |
|--------------------|--------------------|--------------------|-------------------------------|-----------------------------|--------------------|
| | At presentation | At reassessment | At reassessment | At presentation | At reassessment |
| Sensitivity | 55% | 56.8% | 92% | 69% | 82% |
| Specificity | 65% | 65% | 45% | 57% | 57% |
| PPV | 51% | 50% | 40% | 34% | 23% |
| NPV | 68% | 70.9% | 93% | 85% | 91% |

PPV – positive predictive value, NPV – negative predictive value

3.12 Comparison of cohorts

To determine the reasons for the differences in sensitivity and specificity, we compared our cohort to the Ammann¹² and Miedema cohorts³¹ (Table 3.10) and found that our cohort was younger with a median age of 4.7 years compared to 6.9 years for the Ammann cohort¹ and 6.6 years for the Miedema cohort³¹. All three cohorts had a male predominance and similar incidence of both AML (15% in our study population, 11% in the population of Ammann et al¹² and 13% in the population of Miedema et al³¹) and lymphoma (8% in our study population, 8% in the population of Ammann et al¹² and 12% in the population of Miedema et al³¹). ALL was diagnosed in 29% of our cohort, which was lower than the 44% in the cohort of Ammann et al¹² and 37% in the cohort of Miedema et al.³¹ Solid tumours outside the CNS represented 44% of episodes in our cohort, higher when compared to 26% in both the Ammann¹² and Miedema³¹ cohorts. CNS tumours were diagnosed in only 4% of episodes in our cohort, compared to 11% and 12% in the Ammann¹ and Miedema³¹ cohorts, respectively.

Our cohort had more episodes classified as low risk (57%) compared to 35% in the Ammann cohort¹² as well as more AEs in 40% of FN episodes versus 29% in the Ammann cohort¹² and 24% in the Miedema cohort.³¹ Included in the AEs were more SMCs (9%) compared to the cohort of Ammann et al¹² with 4.9% and that of Miedema et al³¹ with 4.7% as well as more MDIs (31%) compared to 22% in the Ammann cohort¹² and 22% in the Miedema cohort³¹ but similar RCP (10%) compared to the cohort of Ammann et al¹² (8.5%). Bacteraemia was also higher in 46% of low-risk FN episodes in our cohort compared to 7% of episodes in the Ammann cohort.³¹ Gram-positive organisms were predominantly isolated in all three cohorts (18% in our cohort vs. 9.9% in the Ammann¹² cohort and 10% in the Miedema³¹ cohort).

AEs were known in 3 episodes at presentation in our cohort compared to 30 episodes known in the Ammann cohort¹². A further 2 episodes were known at reassessment in our cohort compared to 65 in the Ammann cohort¹² and 21 in the Miedema cohort.³¹ Included in the SMCs were three deaths in our cohort, which was similar to three deaths in the Ammann cohort.¹²

Table 3.10: Comparison of the three cohorts

| | Our cohort | | Ammann et al ¹² | | Miedema et al ³¹ | |
|-------------------------------------|------------------|-----------|----------------------------|----|-----------------------------|----|
| | No. | % | No. | % | No. | % |
| FN episodes | 100 | | 423 | | 210 | |
| Patients | 52 | | 206 | | 110 | |
| Median age (years) | 4.7 years | | 6.9 years | | 6.6 years | |
| Male patients | 34 | 65 | 116 | 56 | 63 | 57 |
| Type of cancer | | | | | | |
| ALL | 15 | 29 | 90 | 44 | 41 | 37 |
| AML | 8 | 15 | 23 | 11 | 14 | 13 |
| Lymphoma | 4 | 8 | 16 | 8 | 13 | 12 |
| CNS | 2 | 4 | 23 | 11 | 13 | 12 |
| Solid tumour outside the CNS | 23 | 44 | 54 | 26 | 29 | 26 |

| | | | | | | |
|--|---------------------------|-----------|----------------------------|------|------|-----|
| Median no. of FN episodes/patient | 2 | | 2 | | 1 | |
| Range | 1-5 | | 1-10 | | 1-13 | |
| High risk (Ammann rule) | 43 | 43 | | 75 | | |
| Low risk (Ammann rule) | 57 | 57 | | 35 | | |
| AEs (1 or more) | 40 | 40 | 122 | 29 | 51 | 24 |
| SMC | 9 (including 3 deaths) | 9 | 21 (including 3 deaths) | 4.9 | 10 | 4.7 |
| MDI | 31 | 31 | 94 | 22 | 46 | 22 |
| Bacteraemia | 24 | 24 | 67 | 15.8 | 32 | 15 |
| Bacteraemias in low-risk episodes | | 46 | | 7 | | 29 |
| Gram positive | 18 | 18 | 42 | 9.9 | 22 | 10 |
| <i>S. aureus</i> | 4 (including 1 MRSA) | | 4 | | | |
| Coagulase-negative staphylococci | 1 | | 16 | | 9 | |
| <i>S. mitis</i> | 4 | | 12 | | 8 | |
| Other | 7 | | 14 | | 7 | |
| Gram negative | 13 | 13 | 27 | 6.3 | 11 | 5.2 |
| <i>E. coli</i> | 2 | | 15 | | 3 | |
| <i>P. aeruginosa</i> | 2 | | 6 | | 3 | |
| <i>K. pneumoniae</i> | 6 (including 3 ESBL) | | | | 2 | |
| Other | 3 | | 6 | | 3 | |
| Polymicrobial infection | 3 | 3 | 5 | | 5 | 2.3 |
| RCP | 10 | 10 | 36 | 8.5 | 13 | 6.1 |

| | | | | | | |
|--------------------------|---|--|----|--|----|--|
| AE known at presentation | 3 | | 30 | | | |
| AE known at reassessment | 5 | | 65 | | 21 | |

FN – febrile neutropenia, ALL – acute lymphoblastic leukaemia, AML – acute myeloblastic leukaemia, CNS – central nervous system, AE – adverse event, SMC – severe medical complications, MDI – microbiologically defined infection, RCP – radiologically confirmed pneumonia

3.13 Validation of other risk assessment tools

We thereafter applied the Rackoff,²¹ Baorto,²² Rondinelli²⁷ and Santolaya^{24,25} rules to our patient population to determine whether these could possibly be used to identify a low-risk group. A limitation, however, was the inclusion and exclusion criteria, which could not be applied strictly as there is great variability in the definitions used by the different authors. By applying the Rackoff rule,²¹ 9 episodes were classified as high risk, 61 as mild risk and 28 as low risk while 2 episodes were excluded due to unknown AMC. AEs occurred in 5 high-risk episodes, 25 mild-risk episodes and 10 low-risk episodes. To calculate a sensitivity and specificity, the intermediate- and high-risk groups were combined as the goal of the study was to identify a group at minimal risk of an AE; this yielded a sensitivity of 75% and a specificity of 31%.

The Baorto rule²¹ had a similar performance with 68 episodes identified as high risk (30 AE) and 26 as low risk (8 AE), with a sensitivity of 79% and a specificity 32%. Based on the exclusion criteria, 4 episodes were excluded as the patient's age was below 12 months, with another 2 episodes excluded as the AMC was not known.

The Rondinelli rule²⁷ only included the first FN episode in its calculation of a risk assessment score, and therefore only 52 episodes qualified for inclusion. By applying the rule, 2 episodes were classified as high risk, 10 as intermediate risk and 40 as low risk, with respectively 1, 6 and 15 AEs per group. Again, the high- and intermediate-risk groups were combined to calculate the sensitivity, which was 32%, and the specificity, which was 83%.

The Santolaya rule^{24,25} had a similar performance, achieving a sensitivity of 68% and a specificity of 37%. AEs occurred in 27 of the 68 high-risk episodes and in 13 of the 32 low-risk episodes. We therefore could not achieve an adequate sensitivity or specificity for any of these rules to be applied in clinical practice. Table 11 shows the sensitivity and specificity achieved by applying these rules to our cohort.

Table 3.11: Performance of individual rules in our cohort

| Risk prediction rule | No. of TP | No. of FP | No. of FN | No. of TN | Sens | Spec | NPV | PPV |
|--|-----------|-----------|-----------|-----------|------|------|------|------|
| Rules predicting bacteraemia | | | | | | | | |
| Rackoff et al ²⁰ | 30 | 40 | 10 | 18 | 0.75 | 0.31 | 0.64 | 0.43 |
| Baorto et al ²¹ | 30 | 38 | 8 | 18 | 0.79 | 0.32 | 0.69 | 0.44 |
| Rules predicting severe/invasive bacterial infection | | | | | | | | |
| Rondinelli et al ²⁷ | 7 | 5 | 15 | 25 | 0.32 | 0.83 | 0.63 | 0.58 |
| Santolaya et al ^{24,25} | 27 | 41 | 13 | 19 | 0.68 | 0.37 | 0.59 | 0.40 |

TP – true positive, FP – false positive, FN – false negative, TN – true negative, NPV – negative predictive value, PPV – positive predictive value

Chapter 4: DISCUSSION

4.1 Discussion

This study aimed to validate a risk assessment tool published by Ammann et al¹ that could potentially lead to the identification of a patient population at low risk of suffering an AE during an episode of FN. In the derivation and validation of the Ammann tool,¹² the predefined sensitivity was established at $\geq 90\%$, which was achieved in the researchers' cohort at 92% with an associated 45% specificity, 93% NPV and 40% PPV.¹ This was a similar finding to that reported by Miedema et al,³¹ who also attempted to validate the Ammann rule in a Dutch cohort in 2011 but could only achieve a sensitivity of 82% with a specificity of 57%. Miedema et al proposed that differences in chemotherapy treatment protocols, genetic factors and microbiological environments as well as retrospective collection of their data might be possible reasons for the lower sensitivity.³¹

In this study, the tool was applied prospectively but also yielded significantly lower sensitivity of 55%, specificity of 65%, PPV of 51% and NPV of 68%. This might be explained by the younger age group (4.7 years versus 6.9 years¹²), more severe medical conditions (9% versus 4.9%¹²) and higher bacteraemia (24% versus 15.9%¹²). The Rondinelli rule²⁷ is one of the risk assessment models that include age in its score, with an age of less than five years being associated with an increased risk of SICs, bacteraemia and death ($p = 0.001$).²⁷ Even though the age group in this study was younger than the Ammann cohort,¹ age failed to achieve statistical significant association with an AE ($p = 0.18$).

Ammann et al¹² reported only a 7% bacteraemia rate in their low-risk population, while it was 46% in this study. One of the SMCs that resulted in death occurred in the low-risk group in this study population, which was similar to the study by Ammann et al,¹² who also reported two deaths in patients assessed as low risk at the onset of FN. Other differences included a lower mean Hb level and a higher occurrence of antibiotic-resistant organisms. CNS tumours were more common in the European cohorts.^{12,31} All three cohorts showed a male predominance. Mortality was higher in this study population (3%) compared to the Ammann cohort (0.7%).¹²

We also demonstrated a higher frequency of FN in solid tumours outside the CNS. There were more FN episodes in relapsed malignancies (16%) as well as advanced disease (24%) in this study, which supports the findings of Stones et al that advanced stage of disease contributes to a poorer outcome and higher incidence of AEs.¹³ The mean Hb in our cohort was 8.1 g/dL, lower than the $\text{Hb} \geq 9\text{g/dL}$ used as the highest weighted score in the Ammann rule¹² whereby higher Hb as a risk factor might reflect the need for a blood transfusion prior to presentation with FN.¹² By grading the haematological toxicity of chemotherapy in our patients, we demonstrated that the majority had severe bone marrow suppression at the time of presentation (75% Grade 4 toxicity for WCC, 53% Grade 3 toxicity for Hb and 35% Grade 4 toxicity for platelets), which could contribute to the increased occurrence of AEs with a higher mortality rate. The American Society of Clinical Oncology recommended the use of granulocyte colony-stimulating factor for primary prophylaxis in patients with a high likelihood of FN and as secondary prophylaxis for high-risk patients,⁴⁵ based on a meta-analysis that found a 20% reduction in FN and a shorter hospitalisation duration associated with its use.⁴⁶ Ozkaynak et al found a reduction in the number of days of neutropenia, fever and hospitalisation.⁴⁷ The use of granulocyte colony-stimulating factor was, however, restricted in our cohort and reserved for severe cases of prolonged neutropenia due to limited resources. This could possibly contribute to the higher frequency (40% vs. 29%¹² and 24%³¹) and late occurrence (after reassessment) of AEs.

CRP was the only biomarker of infection routinely available at our institution for identification of bacterial infection and was of limited value, with a high CRP found in both AE and non-AE groups (mean CRP 128 mg/L and 112 mg/L, respectively; $p = 0.42$). This was in keeping with the findings of Miedema et al³⁷ who also demonstrated a minimal difference in median CRP levels in patients with or without bacteraemia ($p = 0.183$) with low sensitivity and specificity in distinguishing bacterial causes of fever from other causes. The researchers concluded that a combination of IL-8 and PCT levels could achieve a sensitivity of 100%.³⁷ In a study conducted by Secmeer et al,³⁶ they could also only demonstrate a sensitivity of 66.7% in the use of CRP to predict bacteraemia in paediatric FN neutropenia, using a CRP cutoff value of 50 mg/L.³⁶ In contrast, Mian et al³⁹ showed a significant difference in median CRP levels in high-risk versus low-risk FN episodes (170 mg/L vs. 38 mg/L) and that a CRP >100 mg/L achieved an 88% sensitivity in predicting FN episodes at high risk of prolonged hospitalisation, ICU admission and MDI.³⁹ A CRP of 178.7 mg/L was shown to be the optimal cutoff value to predict AEs in our patient population with a sensitivity of 71% and a specificity of 83%.

It has been demonstrated that a poor nutritional status contributes to more severe chemotherapy toxicity and a worse long-term outcome in paediatric oncology patients.⁴⁸⁻⁵¹ Specifically, sustained overweight or underweight status during intensive phases of high-risk ALL treatment has been associated with a significantly greater risk for relapse, death or the development of treatment-related toxicity.⁵² We found that most of our patients were within the normal limits according to the WHO classification⁴³ of nutritional status and could therefore not demonstrate a statistically significant association between nutritional status and the occurrence of AEs. A limitation of the study was the lack of data for mid-upper arm circumference or triceps skinfold thickness as measures of malnutrition, which might be more sensitive indicators of malnutrition in paediatric oncology.⁵³

Total WCC ($p < 0.01$) and AMC ($p = 0.05$) were the only variables that reached statistical significance in their independent association with AEs in our cohort, which is in keeping with the findings of both Rackoff et al²⁰ and Baorto et al²¹ in the derivation of their independent rules. The Rackoff rule categorised patients into three categories according to their AMC and temperature at presentation and predicted bacteraemia with a 100% sensitivity and 23.2% specificity.²⁰ When applied to our patient population, the Rackoff rule²⁰ achieved a 42.9% sensitivity and a 64.3% specificity as opposed to the 87% sensitivity and 49% specificity achieved by Ammann et al applying the same rule to their cohort.¹² Baorto et al²¹ modified the Rackoff rule²⁰ using only a monocyte count of $\geq 0.155 \times 10^9/L$ as a predictor of bacteraemia with a sensitivity and specificity of 88.9% and 22.4%, respectively.²¹ Again, this could not be achieved in this study population with a sensitivity of 43.7% and a specificity of 66.7% for the Baorto rule.²¹

The bacterial organism profile of this study group was similar to that of the studies by Ammann et al¹² and Miedema et al,³¹ namely predominantly Gram-positive bacteraemia (73%). Coagulase-negative *Staphylococcus* species was the most common gram-positive organism isolated in both the Ammann¹² ($n = 16$) and Miedema³¹ ($n = 9$) cohorts, which was in contrast to our study population, with *Streptococcus viridans* (20%) being the most common organism. We also documented a higher rate of gram-negative antibiotic-resistant organisms, including four extended-spectrum beta-lactamase-producing *K. pneumoniae* (10%), two methicillin-resistant *S. aureus* (5%) and one *P. aeruginosa* (3%) sensitive only to colistin, while no specific resistance patterns were reported in the Ammann¹² or Miedema³¹ cohorts. The use of ciprofloxacin prophylaxis in the Miedema et al study⁵⁴ showed increased ciprofloxacin resistance in some centres. Ciprofloxacin use is not standard practice at our institution and therefore limited ciprofloxacin resistance (8%) was demonstrated. Because of the small size of

our cohort, it was not possible to determine whether this observed increased resistance pattern was of statistical significance. Resistance to piperacillin-tazobactam was documented in three organisms (8%) (one *E. coli* and two *P. aeruginosa*) in our cohort, with amikacin resistance in the same two *P. aeruginosa* (5%) isolates. Based on the above results, the current empirical antibiotic protocol that includes the use of piperacillin-tazobactam and amikacin as first-line treatment should adequately treat almost 85% (36 of 39) of MDIs.

4.2 Study strengths and limitations

- Data collected prospectively relied on the availability and quality of clinical records created by the admitting physicians and was subject to their choice of words and descriptive terms, thus necessitating conclusions to be drawn and making the data less reliable.
- The outcome of each episode was followed up and documented on a prospective basis, which improved the accuracy and comprehensiveness of the data.

4.3 Conclusion and recommendations

In conclusion, although this study has not succeeded in validating the Ammann tool,¹² it demonstrated the important significant association between total WCC and AMC in an AE during FN. The study also demonstrated the marked differences in patient cohorts between high-income countries versus a low- to middle-income country, especially with regard to median patient age, frequency of FN episodes in solid tumours excluding the CNS as well as the frequent occurrence of antibiotic-resistant bacteraemia. Future studies should include additional biomarkers such as the use of PCT to assist with differentiating between high-risk and low-risk FN.

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Appendix A: Parental informed consent form**PARENT/GUARDIAN INFORMATION LEAFLET AND INFORMED CONSENT FORM FOR CHILDREN 0-15 YEARS FOR CLINICAL STUDY****1. STUDY TITLE**

Predicting the Risk of Adverse Events in Children with Febrile Neutropenia: a validation of previously identified clinical decision rules.

2. INTRODUCTION

Your child has been invited to take part in a research study. The information on this page is to help you decide whether your child will take part. Before you agree to take part in this study you should fully understand what it is about. If you have any questions, which are not fully explained on this page, do not hesitate to ask the study doctor.

3. WHY IS THIS STUDY DONE?

Fever is one of the complications of chemotherapy for cancer. Because chemotherapy decreases your child's ability to fight infection it can cause him/her to become very ill. But infection is not the only cause for fever it can also be the result of the chemotherapy or cancer itself. The aim of this study is to identify factors that could predict serious life threatening infections in children receiving chemotherapy for cancer who also develop a fever. The information obtained will be used to set up a list of factors to predict which patients will be sicker than others. This information will also be used to possibly change monitoring and treatment of children with cancer and fever.

4. EXPLANATION OF PROCEDURES TO BE FOLLOWED

This study involves answering some questions with regards to your child's illness, clinical findings on physical examination and some blood tests. The blood tests will be the same tests routinely done and thus no additional blood samples will need to be collected. The information and results of the blood tests will be captured on a datasheet with a specific study number.

5. HAS THE STUDY RECEIVED ETHICAL APPROVAL?

This clinical study protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Stellenbosch and written approval has been granted by that committee.

6. WHAT ARE YOUR CHILD'S RIGHTS AS A PARTICIPANT IN THIS STUDY?

Your child's participation in this study is entirely voluntary and you can refuse for him/her to take part or withdraw at any time without stating any reason. Your withdrawal will not affect your child's access to continue/other medical care.

7. WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

Vena puncture (i.e. drawing blood) are normally done as part of his/her routine medical care and present a slight risk of discomfort. Drawing blood may result in a bruise at the puncture site, or less commonly swelling of the vein or bleeding from the puncture site. Your child's protection is that the procedures are performed under sterile conditions by experienced personnel.

8. WHAT ARE THE RISKS INVOLVED IN THIS STUDY?

This study will not test any new drugs or procedures so there is no risk related to the study itself. If the tests done show results that are important for the care of the child that information will be given to you and the doctor taking care of your child.

9. CONFIDENTIALITY

All information obtained during the course of this study is strictly confidential. Data that may be reported in scientific journals will not include any information which identifies your child as a patient in this study. Any information uncovered regarding your child's test results or state of health as a result of your child's participation in this study will be held in strict confidence. You will be informed of any finding of importance to your child's health or continued participation in this study. If you have any questions regarding the research study, its aims or procedures you can contact Dr Green or Dr van Zyl at the Tygerberg G3 oncology unit at 021 938 4564. If you have questions regarding your child's rights as a research subject, contact Ms Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] at the Division for Research Development.

INFORMED CONSENT FOR PARENTS / GUARDIANS (On behalf of minors under 15 years old) I hereby confirm that I have been informed by the investigator, Dr about the nature, conduct, benefits and risks of this clinical study. I have also received, read and understood the above written information (Patient Information Leaflet and Informed Consent) regarding the clinical study. I am aware that the results of the study, including my child's personal details regarding date of birth, initials and diagnosis will be anonymously processed into a study report. I may, at any stage, without prejudice, withdraw my consent for my child's participation in the study. I have had sufficient opportunity to ask questions and (of my own free will) declare my child prepared to participate in the study.

.....
Parent/Guardian(s) name
Date.....

.....
Parent/Guardian(s) signature

.....
Patient's name
Date.....

.....
Patient's signature

.....
Researcher's Name
Date.....

.....
Researcher's Signature

Appendix B: Ouertoestemming

OUER/VOOG INLIGTINGSTUK EN INGELIGTE TOESTEMMING VIR KINDERS 0-15 JAAR VIR DIE KLINIESE STUDIE.

1. STUDIE TITEL

Predicting the Risk of Adverse Events in Children with Febrile Neutropenia: a validation of previously identified clinical decision rules

2. INLEIDING

Jou kind is genooi om te deel te neem aan ons navorsingstudie. Die inligting op hierdie bladsy is om jou te help om te besluit of jou kind wat tans siek is, mag deelneem. Voordat u instem om deel te neem in hierdie studie moet u ten volle verstaan waaroor die studie gaan. As u enige vrae het, moet asseblief nie huiwer om die studiedokter te vra nie.

3. HOEKOM WORD DIE STUDIE GEDOEN?

Koors is een van die gevolge van kankerbehandeling (chemoterapie). Koors kan die gevolg van chemoterapie, die kanker self of infeksie wees. Omdat chemoterapie jou kind se vermoë om infeksie te beveg verminder kan dit veroorsaak dat hy/sy baie siek word. Die doel van hierdie studie is om faktore te identifiseer wat ernstige lewensbedreigende infeksies voorspel in kinders wat chemoterapie vir kanker ontvang en 'n koors ontwikkel. Die inligting wat verkry word, sal gebruik word om 'n lys van faktore op te stel wat moontlik sal voorspel watter kinders sieker sal wees as ander. Hierdie inligting sal ook gebruik word om moontlik die monitering en behandeling van kinders met kanker en koors te verander.

4. PROSEDURES WAT GEVOLG GAAN WORD.

Hierdie studie behels die antwoord van 'n paar vrae met betrekking tot jou kind se siekte, kliniese bevindinge op fisiese ondersoek en resultate van bloedtoetse. Die bloedtoetse sal dieselfde toetse wees wat vir opname en behandeling gedoen word. Geen bykomende bloedmonsters sal versamel word nie. Die inligting en resultate van die bloedtoetse sal op 'n datavorm met 'n spesifieke studie nommer ingevul word.

5. ETIESE GOEDKEURING.

Die kliniese studieprotokol is aan die Fakulteit Gesondheidswetenskappe se navorsings-etiekkomitee van die Universiteit van Stellenbosch gestuur en skriftelike toestemming is deur hierdie komitee toegestaan.

6. WAT IS U KIND SE REG AS DEELNEMER AAN DIE STUDIE?

U kind se deelname aan hierdie studie is heeltemal vrywillig en u kan weier dat hy/sy deelneem of u kan enige tyd sonder rede onttrek. Jou onttrekking sal geen invloed op jou kind se voortgesette mediese sorg hê nie.

7. KAN ENIGE VAN DIE PROSEDURES ONGEMAK OF ONGERIEF VEROORSAAK?

Venapunksie (dws om bloed te trek) word gewoonlik gedoen as deel van u kind se roetine mediese sorg en bied 'n risiko van ongemak. Om bloed te trek kan lei tot 'n kneusing (blou kol) op die punksie area, of minder algemeen swelling van die aar of bloeding van die punksie area. Jou kind se beskerming is dat die prosedures uitgevoer word onder steriele omstandighede deur ervare personeel. Slegs die roetine toetse sal gedoen word – dws GEEN addisionele bloedmonsters sal geneem word nie.

8. WAT IS DIE RISIKO VIR U KIND AS DEELNEMER VAN DIE STUDIE?

Hierdie studie sluit NIE die toets van enige nuwe medisyne of prosedures in nie, so daar is geen risiko verbonde aan die studie self nie. As die toetse gedoen enige resultate belangrik vir die versorging van u kind toon, sal die inligting aan u gegee word deur die dokter wat na u kind omsien.

9. **VERTROULIKHEID.**

Alle inligting wat in die loop van hierdie studie versamel word, is streng vertroulik. Data wat moontlik in wetenskaplike tydskrifte berig word, sal nie enige inligting insluit wat u kind as 'n pasiënt in hierdie studie kan identifiseer nie. Enige inligting rakende u kind se toetsuitslae of staat van gesondheid sal streng vertroulik hanteer word. U sal in kennis gestel word van enige bevinding van belang vir u kind se gesondheid of behandeling. As jy enige vrae oor die navorsing, sy doelwitte of prosedures het kan jy Dr Green of Dr van Zyl by die Tygerberg G3 onkologie-eenheid by 021 938 4564 kontak. As jy enige vrae het oor jou kind se regte as 'n studiedeelnemer, kontak me Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] by die Afdeling Navorsingsontwikkeling.

INGELIGTE TOESTEMMING VIR OUIERS / VOOGDE (Namens minderjariges onder 15 jaar) Ek (.....) bevestig hiermee dat ek ingelig is deur die ondersoeker, dr oor die aard, optrede, voordele en risiko's van hierdie kliniese studie. Ek het ook (ontvang, gelees en verstaan) die bogenoemde skriftelike inligting ten opsigte van die kliniese studie ontvang, gelees en verstaan. Ek is bewus daarvan dat die resultate van die studie, insluitend my kind se persoonlike besonderhede met betrekking tot die datum van geboorte, voorletters en diagnose anoniem verwerk sal word in 'n studieverslag. Ek kan in enige stadium, sonder vooroordeel, my toestemming vir my kind se deelname aan die studie onttrek. Ek het voldoende geleentheid gekry om vrae te vra en (van my eie vrye wil) gee ek toestemming dat my kind mag deelneem aan die studie.

| | |
|-------------------|----------------------------|
| | |
| Ouer/voog se naam | Ouer/ voog se handtekening |

.....
Datum

| | |
|-----------------|-------------------------|
| | |
| Pasiënt se naam | Pasiënt se handtekening |

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Datum

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| | |
| Navorser se Naam | Navorser se handtekening |

.....
Datum

| | |
|------------------|--------------------------|
| | |
| Navorser se Naam | Navorser se handtekening |

.....
Datum

Appendix C Xhosa parental consent

Isihlomelo C: Uxwebhu lwemvume efanelekileyo yomzali.

IPHETSHANA LEENKCUKACHA ZOMZALI/ZOMNTU OKHULISA UMNTWANA NGOKUSEMTHETHWENI KUNYE NOXWEBHU LWEMVUME EFANELEKILEYO YABANTWANA ABASUSELA KWI-0-15 LEMINYAKA UBUDALA KUPHANDO LWEZONYANGO

10. ISIHLOKO SOPHANDO

Xa sithekelela uMngcipheko weZiganeko eziNgathandekiyo kuBantwana abanesifo esiya-Febrile Neutropenia: IMigaqo yeSiqinisekiso seSigqibo esenziwa Ngaphambili kuNyango (A Validation of Previously Identified Clinical Decision Rules.)

11. INTSHAYELELO

Umntwana wakho umenyiwe ukuba athathe inxaxheba kuphando lwesifundo. Iinkcukacha ezikweli phepha zezokukunceda ukuba wenze isigqibo ngokuba ingaba umntwana wakho uza kuthatha inxaxheba kolu phando kusini na. Phambi kokuba uvume ukuthatha inxaxheba kolu phando kufuneka uqonde ngokupheleleyo ukuba lumalunga nantoni na. Ukuba unemibuzo, engacaciswa ngokupheleleyo kweli phepha, ungathandabuzi ukubuza ugqirha wophando.

12. LWENZELWA NTONI OLU PHANDO?

Ifiva sesinye sezigulo ezinobucubhede xa kusenziwa unyango lomhlaza ngokutshisa ngoomatshini ikhimotheraphi. Ngenxa yokuba ikhimotheraphi icutha amandla omntwana wakho okulwa nolosuleleko zizifo oko kungambangela ukuba agule kakhulu. Kodwa ulosuleleko zizifo ayikokuphela konobangela wefiva kusenokuba sisiphumo sekhimotheraphi okanye somhlaza ngokwawo. Injongo yolu phando kukuchonga iimpawu ezinokukhokelela kulosuleleko zizifo eziyingozi emandla ebomini babantwana abafumana unyango lwekhimotheraphi kwisifo somhlaza nothi abe nefiva. Iinkcukacha ezifunyenweyo ziya kusetyenziselwa ukuqulunga uluhlu lwempawu ezinkuthekelelwa ukuba zizo ezinokubonisa ukuba ziziphi izigulana eziya kugula kakhulu kunezinye. Kananjalo ezi nkcukacha ziya kusetyenziselwa mhlawumbe ukutshintsha indlela abajongwa ngayo nabanyangwa ngayo abantwana abanomhlaza nefiva.

13. INGCACISO YEENKQUBO EZIZA KULANDELWA

Olu phando luquka ukuphendula imibuzo ethile ephathelene nokugula komntwana wakho, iziphumo zonyango zohlolo lomzimba nezinye iimvavanyo zegazi. Iimvavanyo zegazi ziya kuba ziimvavanyo ezifanayo ezenziwa ngokwesiqhelo kwaye ke ngenxa yoko akusayi kufunwa zisampuli zongeziweyo zegazi.

Iinkcukacha neziphumo zazo zonke iimvavanyo zegazi ziya kugcinwa kuvimba weenkcukacha onenombolo ethile yophando.

14. INGABA OLU PHANDO LUSIFUMENE ISIPHUMEZO SOKWAMKELEKA NGOKWEENQOBO EZISESIKWENI?

Le migaqo yophando lwezonyango yangeniswa kwiKomiti yeeNqobo ezisesikweni ngoPhando yeCandelo lobuNzululwazi ngezeMpilo, kwiYunivesithi yase-Stellenbosch kwaye kwanikezelwa isiphumezo esibhaliweyo yile komiti.

15. NGAWAPHI AMALUNGELO OMNTWANA WAKHO NJENGOMTHATHI-NXAXHEBA KOLU PHANDO?

Ukuthatha inxaxheba komntwana wakho kolu phando kwenziwa ngokuzithandela ngokupheleleyo kwaye unelungelo lokungavumi ukuba athathe inxaxheba okanye

ungamkhupha nanini na ngaphandle kokubeka isizathu soko. Ukurhoxa kwakho akusayi kuchaphazela indlela yokufikelela komntwana wakho kunyango lwamayeza oluqhubekayo okanye kolunye unyango.

16. INGABA KUKHO INKQUBO KWEZI ZOLU PHANDO ENOKUKHOKHELELA EKUBENI UNGAZIVA KAKUHLE OKANYE UPHAZAMISEKE?

I-Vena puncture (umzekelo: ukutsalwa kwegazi) kudla ngokwenziwa ngokuyinxalenye yonyango lwakhe lwesiqhelo kwaye kwenza ungaziva kakuhle kancinane nje. Ukutsalwa kwegazi kungakhokelela ekubeni nomtshithana kule ndawo bekutsalwa kuyo igazi, okanye ukudumba okuncinane okuqhelekileyo komthambo okanye ukopha kule ndawo bekutsalwa kuyo igazi. Ukuseleko lomntwana wakho kukuba ezi nkqubo zenziwa phantsi kweemeko engenantsholongwane kwaye isenziwa ngabasebenzi abanamava.

17. YIYIPHI IMINGCIPHEKO EBANDAKANYEKA KOLU PHANDO?

Olu phando alusayi kuvavanya nawaphi amachiza amatsha okanye iinkqubo ezintsha ngoko ke akukho mngcipheko onxulumene nophando olu ngokwalo. Ukuba iimvavanyo ezenziweyo zibonakalisa iziphumo ezibalulekileyo ekukhathalelweni komntwana ezi nkukacha ziya kunikezelwa kuwe nogqirha onyanga umntwana wakho.

18. UKUGCINWA KWEENKCUKACHA ZIYIMFIHLO

Zonke iinkcukacha ezifunyenwe ngexesha lolu phando ziya kugcinwa ziyimfihlo ngokumandla. Iinkcukacha ezinokukhankanywa kumaphepha-ndaba obunzululwazi azisayi kubandakanya zaziphi iinkcukacha ezinokwalatha umntwana wakho njengesigulana kolu phando. Naziphi iinkcukacha ezingajongwanga ngokuphathelelene neziphumo zovavanyo okanye nemeko yempilo yomntwana wakho ngenxa yokuthatha inxaxheba komntwana wakho kolu phando ziya kugcinwa ziyimfihlo ngokumandla. Uya kwaziswa ngazo naziphi iziphumo ezibalulekileyo ngempilo yomntwana wakho okanye ngokuqhubeka ethatha inxaxheba kolu phando.

Ukuba unemibuzo enxulumene nolu phando, iinjongo okanye iinkqubo zalo uvumelekile ukuqhagamshelana noGqr. Green okanye uGqr. van Zyl kwiCandelo loNyango lwezifo ezinxulumene namathumba kwa-G3 eTygerberg (Tygerberg G3 Oncology Unit) kwa-021 938 4564.

Ukuba unemibuzo enxulumene namalungelo omntwana wakho njengomntu osetyenziswa kuphando, qhagamshelana noNkskz. Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] kwiCandelo loPhuhliso loPhando.

IMVUME EFANELEKILEYO YABAZALI / YABANTU ABAKHULISA UMENTWANA NGOKUSEMTHETHWENI

(egameni labantwana abangaphantsi kweminyaka eli-15 ubudala)

Mna ngenxa yoko ndiqinisekisa ukuba ndazisiwe ngumphandi,

uGqr..... ngohlobo, indlela oluqhutywa ngayo, iinzuzo nemingcipheko yolu phando lwezonyango. Kananjalo ndifumene, ndafunda ze ndaqonda zonke iinkcukacha ezibhalwe apha ngasentla (kwiPhetshana leeNkcukacha zeSigulana kunye neMvume eFanelekileyo) ezinxulumene nolu phando lwezonyango. Ndiyazi ukuba iziphumo zolu phando, kuqukwa iinkcukacha zomntwana wam buqu eziphathelelene nomhla wokuzalwa,

onobumba bokuqala bamagama akhe neziphumo zokuxilongwa kwakhe ziya kuqwalaselwa kungaziwa ukuba zezikabani kwingxelo yophando.

Ndinakho ukuthi, nanini na, ngaphandle kokugwetywa, ndiyirhoxise invume yam yokuthatha inxaxheba komntwana wam kolu phando. Ndibe nethuba elaneleyo lokubuza imibuzo (ngokuzithandela kwam) kunye nokwazisa ukuba umntwana wam ukulungele ukuthatha inxaxheba kolu phando.

| | |
|-------------------------------|-----------------------------------|
| | |
| Igama lomzali/lomntu okhulisa | Utyikityo lomzali/lomntu okhulisa |
| umntwana ngokusemthethweni | umntwana ngokusemthethweni |
| | |
| Umhla..... | |
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| Igama lesigulana | Utyikityo lwesigulana |
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| Umhla..... | |
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| Umhla..... | |

Appendix D Child assent form



CHILD ASSENT FORM

I am Dr Green from Stellenbosch University. I am doing a research study to figure out why some children with cancer become sicker than others. We are asking you to take part in the research study because with the information we collect we might be able to help you and other children to get better. It will also help us to better understand what happens to you when you become sick.

For this research, we will use information of your cancer type and treatment, current illness and results of blood and other tests. We will keep all your information private, and will not show it to anybody not directly involved in the research. Only people from Stellenbosch University working on the study will see it.

Because you are currently sick and have a fever, blood and other tests will be done to help you get better. We will not do any other tests. We will only use the information (and test results) from your folder in our research.

With the information we collect from your records, we might be able to better help you and other children in the future. Using this information we hope to predict which children will become sicker than others, thus making it possible to help them sooner.

You should know that:

- You do not have to be in this study if you do not want to. You won't get into any trouble if you say no.
- You may stop being in the study at any time.
- Your parent(s)/legal guardian(s) were asked if it is OK for you to be in this study. Even if they say it's OK, it is still your choice whether or not to take part.
- You can ask any questions you have, now or later. If you think of a question later, you or your parents/legal guardian(s) can contact us.

- If you have any questions regarding the research study, its aims or procedures you or your parents can contact Dr Green or Dr van Zyl at the Tygerberg G3 oncology unit at 021 938 4564.
- If you have questions regarding your rights as a research subject, contact Ms Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] at the Division for Research Development.

Sign this form only if you:

- Have understood what you will be doing for this study,
- Have had all your questions answered,
- Have talked to your parent(s)/legal guardian(s) about this project, and
- Agree to take part in this research

Your Signature

Printed Name

Date

Name of Parent(s) or Legal Guardian(s)

Researcher Signature

Printed Name

Date

Appendix E Kinderinstemmingsvorm



Kinderinstemmingsvorm

Ek is Dr Green van Stellenbosch Universiteit. Ek is besig om 'n navorsingsprojek te doen om uit te vind hoekom sekere kinders met kanker sieker word as ander. Ons wil graag hê jy moet deelneem aan ons projek sodat ons jou and ander kinders met kanker kan help om beter te word en ook sodat ons jou siekte beter kan verstaan.

Omdat jy nou siek is met 'n hoë koors gaan die dokters bloed trek en ander toetse doen om jou te help om beter te word. Ons wil graag die inligting van jou siekte en die uitslae van jou toetse gebruik. Jou inligting sal 'n geheim bly en niemand behalwe die mense betrokke by die projek sal dit sien nie.

Met die inligting wat ons versamel van jou en ander kinders wat aan ons projek deelneem, wil ons kyk of ons kan voorspel watter kinders sieker gaan word as ander. Op hierdie manier kan ons kinders met dieselfde siekte help om nie sieker te word nie.

Jy moet weet dat:

- Dit jou keuse is om aan ons projek deel te neem en indien jy nie sou wou deelneem nie, jy nie in die moeilikheid sal kom nie.
- Jy enige tyd kan kies om nie deel te neem of om te onttrek van ons projek.
- Ons met jou ouers/voog gepraat het en dit OK is met hulle dat jy deelneem.

- Jy enige vrae kan vra, nou of later. As jy eers later aan iets dink kan jy of jou ouers/voog ons kontak.
- As jy enige vrae oor die navorsing, sy doelwitte of prosedures het, kan jy of jou ouers Dr Green of Dr van Zyl by die Tygerberg G3 onkologie-eenheid by 021 938 4564 kontak.
- As jy enige vrae het oor jou regte as 'n studiedeelnemer, kontak me Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] by die Afdeling Navorsingsontwikkeling.
-

Teken net hierdie vorm:

- As jy verstaan waaroor die projek gaan.
- As al jou vrae beantwoord is.
- As jy met jou ouers/voog gepraat het oor jou deelname aan ons projek.
- As jy aan ons projek wil deelneem.

Jou handtekening

Naam en Van

Datum

Naam van Ouer of Voog

Navorser se Handtekening

Naam en Van

Datum

Appendix F Xhosa child assent form



UXWEBHU LWEMVUME YOMNTWANA

NdinguGqr. Green weYunivesithi yase-Ştellenbosch. Ndenza uphando ukufumanisa ukuba kutheni abanye abantwana abanesifo somhlaza begula kakhulu kunabanye. Şicela ukuba uthathe inxaxheba kolu phando kuba ngeenkcukacha esiziqokelelayo singanakho ukukunceda wena nabanye abantwana nibe ngcono. Kananjalo kuya kusanceda ukuba siqonde ngcono ukuba kwenzeka ntoni kuwe xa ugula.

Ngeenjongo zolu phando, siza kusebenzisa iinkcukacha zohlobo lwesifo sakho somhlaza nonyango, isigulo esikhoyo kunye neziphumo zovavanyo lwegazi nezinye iimvavanyo. Şiza kugcina zonke iinkcukacha zakho ziyimfihlo, kwaye asisayi kuzibonisa nabani na ongabandakanyeki ngqo kolu phando. Ngabantu abavela kwiYunivesithi yase-Ştellenbosch kuphela abasebenza kolu phando abaya kuzibona.

Ngenxa yokuba uyagula ngoku kwaye unefiva uvavanyo lwegazi nezinye iimvavanyo ziya kwenziwa ukukunceda ube ngcono. Asisayi kwenza ezinye iimvavanyo nokuba zezantoni na. Şiza kusebenzisa kuphela iinkcukacha (kunye neziphumo zovavanyo) ezikuxwebhu lweenkcukacha zempilo yakho kuphando lwethu.

Ngolwazi esilufumana kwiinkcukacha zakho ezigciniweyo, singakwazi ukukunceda ngcono nabanye abantwana kwixesha elizayo. Ngokusebenzisa ezi nkcukacha sinethemba lokuthekelela ukuba ngabaphi abantwana abaza kugula kakhulu kunabanye, ngalo ndlela kube nzima ukubanceda ngokukhawuleza.

Kufuneka wazi ukuba:

- Akunyanzelekanga ukuba uthathe inxaxheba kolu phando xa ungafuni. Awusayi kungenxa ngakini nangayiphi na indlela ukuba uthi hayi.
- Uvumelekile ukuyeka ukuthatha inxaxheba kolu phando nangaliphi na ixesha.
- Abazali bakho/abantu abakukhulisayo ngokusemthethweni babuzwa ukuba ingaba KULUNGILE na ukuba ubandakanywe kolu phando. Nokuba bona bathe KULUNGILE, kusejilungelo lakho ukuzikhethela ukuba uyafuna ukuthatha inxaxheba okanye awufuni kusini na.
- Uvumelekile ukubuza nayiphi imibuzo onayo, ngoku okanye kamva kolu phando. Ukuba uthe wacinga umbuzo kamva, wena okanye abazali bakho/abantu abakukhulisayo ngokusemthethweni bavumelekile ukuqhagamshelana nathi.
- Ukuba unayo nayiphi imibuzo ephathelene nolu phando, iinjongo okanye iinkqubo zalo wena okanye abazali bakho bangaqhagamshelana noGqr. Green okanye uGqr. van Zyl kwicandelo lonyango lwezifo ezinxulumene namathumba kwa-G3 eTygerberg (Tygerberg G3 oncology unit) kule nombolo yomnxeba: 021 938 4564.
- Ukuba unemibuzo enxulumene namalungelo akho njengomntu ekwenziwa kuye uphando, qhagamshelana noNksz. Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] kwiCandelo loPhuhliso loPhando.

Tyikitya olu xwebhu kuphela ukuba:

- Uyiqondile into oza kulwenzela yona olu phando,
- Iphendulekile yonke imibuzo yakho,
- Uthethile nabazali bakho/nabantu abakukhulisayo ngokusemthethweni malunga nolu phando, kwaye
- Uyavuma ukuthatha inxaxheba kolu phando

Utyikityo lwakho Igama elibhalwe ngoonobumba Umhla

Igama lomzali okanye lomntu okukhathalelayo ngokusemthethweni

Utyikityo loMphandi Igama elibhalwe ngoonobumba Umhla

Appendix G Data collection sheet**Part 1**

| | | | |
|--|----------|---------------------|--|
| Patient folder number | | | |
| Study number | | | |
| Date of admission | | | |
| Number of days admitted before FN episode | | | |
| Patient related parameters | | | |
| Age | | | |
| Gender | Male | Female | |
| Temperature | | | |
| Pulse rate | | | |
| Respiratory rate | | | |
| Blood pressure | | | |
| Percutaneous oxygen saturation | | | |
| Capillary refill time | | | |
| Nutritional status | W | L | |
| Clinical focus of infection | | | |
| Comorbidities | | | |
| | | | |
| Disease related parameters | | | |
| Presence of a central venous catheter | Yes | No | |
| Type of central venous catheter | Broviac | Port | |
| Type of malignancy | | | |
| Phase of chemotherapy | | | |
| Number of days since last chemotherapy | <7 days | >7days | |
| Biomarkers | | | |
| Haemoglobin | | Hb \geq 90g/dl(5) | |
| Leucocyte count | | L<0.3g/dl(3) | |
| ANC | | | |
| AMC | | | |
| Platelet count | | Plt<50g/dl(3) | |
| CRP | | | |
| PCT | | | |
| Blood culture result | Positive | Negative | |
| Organism | | | |
| Sensitivity | | | |
| CXR-radiologically confirmed pneumonia | Yes | No | |
| Other cultures | | | |
| Urine | Positive | Negative | |
| Organism | | | |
| Sensitivity | | | |
| CSF | Positive | Negative | |
| Organism | | | |
| Sensitivity | | | |

| | | |
|--|-----------------|---------------|
| Other | | |
| Chemotherapy more intensive than ALL maintenance | Yes (4) | No |
| Total Prediction Score | >/= 9 | < 9 |

| | | |
|---|------------------------|--------|
| Part 2 | | |
| Outcome before/at 24hours | | |
| SMC (Serious medical complication) | Death | |
| | ICU admission | |
| | Life threatening event | |
| MDI (Microbiologically defined infection) | Positive blood culture | |
| | Positive urine culture | |
| | Positive CSF culture | |
| | Positive other culture | |
| Radiologically defined pneumonia | Present | Absent |

| | | |
|--|------------------------|--------|
| Outcome during admission | | |
| Number of days since presentation at time of A/E | | |
| SMC | Death | |
| | ICU admission | |
| | Life threatening event | |
| MDI | Positive blood culture | |
| | Positive urine culture | |
| | Positive other culture | Absent |
| Radiologically defined pneumonia | Present | |

| | | |
|---|------------------------|--------|
| Outcome at follow up | | |
| Number of days since presentation to at time of A/E | | |
| SMC | Death | |
| | ICU admission | |
| MDI | Positive blood culture | |
| | Positive urine culture | |
| | Positive other culture | Absent |
| Radiologically defined pneumonia | Present | |
| No adverse event | | |

Appendix H NHLS blood culture protocol**BLOOD CULTURES - COLLECTION AND TRANSPORT**

We recommend that a minimum of 2 blood cultures from different sites should be submitted in order to acquire the optimal volume of blood and to facilitate the interpretation of results. Anaerobic blood cultures are not available routinely. This test is not cost effective due to low number of requests and high cost.

1. PROCEDURE**Site selection.**

The phlebotomist should:

- Select a different site for each blood sample.
- Avoid drawing blood through indwelling intravenous or intra-arterial catheters. However if blood cultures have been obtained from intravascular catheters, they should be labelled as such and one set of blood cultures should also be obtained by venipuncture at the same time in order to help assess positive blood cultures from catheters.

Site preparation.

- Vigorously cleanse the venipuncture site with 70% isopropyl or ethyl alcohol and wait till dry.
- Apply 2% tincture iodine or povidone-iodine in ever increasing circles starting at point where venipuncture is to be made. Note: A contact time of 1.5-2 minutes after swabbing is necessary for optimal disinfection.
- Do not touch the venipuncture site after preparation and prior to phlebotomy.
- Disinfecting blood culture bottles.
- Disinfect the top of the bottle or tube with alcohol and allow top to dry.

Collection of blood.

- Using syringe and needle insert the needle into the vein, and withdraw blood. Do not change needles before injecting the blood into the culture bottle due to risk of a needle stick injury.
- After the blood is inserted into the blood culture system mix well to avoid clotting.
- Use a new needle if vein is missed initially.
- Add sufficient volume of blood to attain a 1:10 ratio of blood to medium (the volume of blood required is indicated by the manufacturer on the bottle).
- After phlebotomy, cleanse the site with 70% alcohol to remove remaining iodine, which can cause irritation in some patients and cover puncture wound appropriately.

2. SPECIMEN VOLUME

Note: The volume of blood is critical because the number of organisms in the majority of bacteraemia is low, especially if the patient is on antimicrobial therapy. In infants and children, the number of microorganisms during bacteraemia is higher than in adults; therefore, less blood is required for culture. Recommended volume per bottle: see label on bottle.

Children: Ideally, 3 to 5ml of blood should be added to bottle.

Neonates: 1-3ml of blood per bottle.

Adults: Ideally 10ml blood per culture bottle (aerobic).

3. RECOMMENDATION ON NUMBER AND TIMING OF BLOOD CULTURES

4. A minimum of 20ml (one set consisting of two aerobic bottles) is recommended in order to get an optimal yield from blood cultures. It may be desirable to collect sets over 3 consecutive days in patients who have been on antimicrobial therapy.
5. Fever of unknown origin (occult abscess, typhoid fever, or brucellosis): Obtain two separate samples initially. It is recommended that a further 2 samples be obtained during temperature spike ideally after 24-36 hours of the initial samples. The increase in positive cultures beyond four cultures is very minimal.
6. Suspected endocarditis – collection of blood cultures do not have to coincide with fever spikes due to continuous bacteraemia.

BOTTLE TYPES:

| BOTTLE | USE | BLOOD VOLUME |
|---|---|---|
| Standard Aerobic Culture Bottles (Blue caps) – available in wards | These bottles are generally used in most of the bacteraemia and fungaemia cases | The optimal blood volume per bottle for culture is 8-10ml. |
| Paediatric Culture Bottles (Yellow caps) – available in wards | These bottles are aerobic and are used for low volume specimens; such as in neonates | The optimal blood volume per bottle for culture is 1-3ml |
| Resin containing Aerobic Culture Bottles (Grey caps) – obtainable from lab | The resin bottles absorb antibiotics and the inhibiting components out of the blood; enhancing the recovery of micro- organisms. | The optimal blood volume per bottle for culture is 8-10ml.. |
| Myco/F lytic (Mycobacteria, fungi) (red cap) – obtainable from lab | These bottles are generally used in cases of disseminated TB; M. avium-intracellulare and systemic fungal infections. Candida and Cryptococcus will grow well in standard aerobic | The optimal blood volume per bottle for culture is 1-5ml. |

| | | |
|--|----------|--|
| | bottles. | |
|--|----------|--|

DURATION OF INCUBATION :

TBH incubates blood cultures for 5-7 days; using an automated system. When fastidious organisms are suspected as a cause of sepsis or infectious endocarditis, e.g. HACEK organisms (*Haemophilus aphrophilus*/*paraphrophilus*, *Actinobacillus actionmycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*), the laboratory should be notified of this possibility, so that the blood culture can be incubated for a longer time (14 days). Suspected *Brucella* is incubated for 28 days and suspected TB and fungi are incubated for 42 days, before the culture is regarded as negative.

QUALITY CONTROL:

Media

5. Check expiry dates of each batch of blood culture bottles used.
6. Uninoculated blood culture bottles should be stored in a cool dark place
7. Examine bottles for turbidity and/or change of colour before adding any blood.
8. Discard any bottles showing abnormal characteristics.

Labelling and transport.

Please ensure that all blood culture bottles are labelled correctly (not over bar code) and that the request form is completed with all the relevant required data. All specimens should be transported to the laboratory promptly. Failure to do this may result in the death of fastidious organisms and in overgrowth by more hardy bacteria.¹

¹ NHLS Tygerberg Microbiology Specimen Sampling Manual, January 2006.

Appendix I Febrile neutropenia hospital treatment protocol.**FEVER:**

- $>38,5^{\circ}\text{C}$ 1x/24hours
- or $>38^{\circ}\text{C}$ 2x/24hours

EXAMINATION: Skin (especially Broviac/port site, LP and bone marrow lesions), peri-anal, mouth and lungs.

INFECTION WORK UP:

- Blood culture (always): repeat culture if temperature stays high ($>38^{\circ}\text{C}$) NB if a positive culture is found, another culture must always be repeated after the infection has been treated. Remember to tick off MCS & fungal culture on the request form.
- FBC and differential count (always)
- CRP(always)
- Urine & stool MCS if indicated
- Blood chemistry if indicated
- Urgent CXR if respiratory problems
- Throat swab if clinically indicated
- LP if clinically indicated
- Other imaging as indicated
- Virus screening and other appropriate investigations where necessary
- Consider echo in case of prolonged fever

- FBC: If ANC (Absolute Neutrophil Count) >500 ($0.5 \times 10^9/\text{l}$), please do an infection work up and consider prescribing an oral broad spectrum antibiotic if clinically indicated.
- Treatment of fever if ANC <500 ($0.5 \times 10^9/\text{l}$):
 - Pip-Taz 50mg/kg/dose 6 hourly
 - Amikacin 1 week to 10 years: 25mg/kg on day 1, then 18mg/kg daily. >10 years: 20mg/kg on day 1, then 15mg/kg daily (max dose 1,5g) .
 - If mucositis present or Staphylococcal infection suspected, also add vancomycin 10mg/kg/dose 6 hourly

Note: patients with an indwelling central line and fever should get an infection work-up and receive IV antibiotics.

If no improvement within 24 - 48 hours or if a Staphylococcus infection (Gram positive) is suspected, add:

Vancomycin 10 mg/kg/dose 6 hourly (max. = 3g/d)
 Monitor blood levels of Amikacin and Vancomycin
Aminoglycoside levels (Therapeutic)

| | Amikacin | Vancomycin |
|------|----------|------------|
| Pre | <10 | 5 - 10 |
| Post | 20 - 36 | 15 - 25 |

Consider change of Piptaz to the following antibiotics if extended spectrum organisms are suspected:

Meropenem (20-40 mg/kg/dose 8 hourly) (weight >50 kg: 1 g 8 hourly)
 or Ciprofloxacin 10mg/kg/dose (max 400mg) 8 hourly

Please note:

- i. If patient has an indwelling catheter (Broviac) consider Vancomycin after 24 hours.
- ii. *If patient is acutely ill or considered to be infected by a possible hospital acquired organism, start with Meropenem.*

If patient is still feverish after 5-7 days, add anti-fungus treatment as follows:

1. Fluconazole: - mainly prophylaxis and treatment of GIT candidiasis

6 mg/kg/day prophylactic
 6-12 mg/kg/day for systemic infection
 3 mg/kg/day for mucositis

2. Amphotericin-B – if proof of fungal infection:

Dose: Start with test dose of 0,1 mg/kg

If well tolerated, continue with 0.6-1 mg/kg/day or alternative days over 6-8 hours. (discuss on ward round)

Monitor urea, creatinine and electrolytes.

Potassium supplementation is almost always necessary

Phenergan is sometimes necessary before Amphotericin infusion.

Possibility of removal of broviac catheter must be discussed with consultant in the following cases:

- *Fungal infection*
- *Second positive blood culture after course of antibiotics completed*
- *Repeated infections with the same organism*
- *Broviac tunnel infection*

b. OTHER DOSAGES

- Ciprofloxacin: 10-20 mg/kg/dose 12 hourly PO or 10mg/kg/dose (max 400mg) 8 hourly IV
- Ceftriaxone 25-100 mg/kg/day IV
- Cefuroxime 30-100 mg/kg/day ÷ 3 IV or <2yr 125 mg 2x/day, >2yr 250 mg 2x/day PO
- Colistin 40 000U/kg 8 hourly IV (needs MCC approval)
- Cyclocapron: 15-25 mg/kg/dose 6-8 hourly PO or IV (tablets = 500 mg)
- Fluconazole: 3-12 mg/kg/day but 8 mg/kg loading dose for systemic infection
- Meropenem: 20-40 mg/kg 8hrly (weight > 50Kg : 1 g 8hrly)
- Imipenem 50 mg/kg/day